FORMULATION AND EVALUATION OF PALIPERIDONE SUSTAINED RELEASE TABLETS USING NATURAL GUMS AS BINDER

Dissertation submitted to

The Tamilnadu Dr. M.G.R Medical University, Chennai

In partial fulfillment for the award of the Degree of

MASTER OF PHARMACY

(Pharmaceutics)

MARCH-2014

DEPARTMENT OF PHARMACEUTICS

KMCH COLLEGE OF PHARMACY

KOVAI ESTATE, KALAPPATTI ROAD,

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Reg.No: 261210901

Under the Guidance of

Dr. K.S.G. ARUL KUMARAN, M. Pharm., Ph.D.,
Head of the Department

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CERTIFICATE

This is to certify that the work as embodied in the dissertation entitled **"FORMULATION AND EVALUATION OF PALIPERIDONE SUSTAINED RELEASE TABLETS USING NATURAL GUMS AS BINDER"** submitted by **Reg. No: 261210901** is a bonafide work carried out by the candidate under the guidance of **Dr. K.S.G. Arulkumaran, M.Pharm., Ph.D.,** to The Tamil Nadu Dr. M.G.R. Medical University**,** Chennai, in partial fulfillment for the Degree of **Master of Pharmacy in Pharmaceutics** at the Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore, Tamil Nadu during the academic year 2013-2014.

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CERTIFICATE

This is to certify that the project work entitled **"FORMULATION AND EVALUATION OF PALIPERIDONE SUSTAINED RELEASE TABLETS USING NATURAL GUMS AS BINDER"** was carried out successfully by **Reg. No: 261210901.** The work mentioned in this dissertation was carried out at the Department of Pharmaceutics, K.M.C.H College of Pharmacy, Coimbatore – 641048, under the guidance of **Dr. K.S.G. Arulkumaran, M.Pharm., Ph.D.,** in partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmaceutics** during the academic year 2013-2014.

Date:
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Head of the Department
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DECLARATION

I hereby declare that this dissertation entitled **"FORMULATION AND EVALUATION OF PALIPERIDONE SUSTAINED RELEASE TABLETS USING NATURAL GUMS AS BINDER"** submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment for the award of Degree of **Master of Pharmacy in Pharmaceutics** was done by me under the institutional guidance of **Dr. K.S.G. Arulkumaran, M. Pharm., Ph.D.,** Head of the Department, Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore, during the year 2013 – 2014.

Date: **Reg. No: 261210901**

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EVALUATION CERTIFICATE

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Examination Centre: KMCH College of Pharmacy, Coimbatore.

Date:

Internal Examiner **External Examiner**

Convener of Examination

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I dedicate myself before the unfailing presence of **GOD** and constant love and encouragement given to me by my beloved Father **E.M. BRAHMADATHAN NAMBOOTHIRIPAD**, my mother **GOWRY V.A.,** my sister **ANURADHA** and my remaining family members who deserve the credit of success in whatever work I did.

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ABBREVIATIONS USED

e.g.	Example
i.e.	That is
%	Percentage
Kg.	Kilogram
gm.	Gram
mg.	Milligram
µg.	Micro gram
ml.	Milliliter
cm.	Centimeter
mm.	Millimeter
nm.	Nanometer
^{w}/w	Weight by weight
^{w}/v	Weight by volume
avg.	Average
hrs.	Hours
pH.	Hydrogen ion concentration
^{o}C	Degree centigrade
RH.	Relative Humidity
HCl	Hydrochloric acid
RPM.	Revolution per minute
Abs.	Absorbance
Conc.	Concentration
Fig.	Figure
UV-VIS	Ultra violet and visible spectroscopy
FTIR	Fourier Transform Infrared spectroscopy
C.I	Compressibility Index
CR	Cumulative Release
SR	Sustained Release
USP	United State Pharmacopoeia
BP	British Pharmacopoeia
R^2	Regression coefficient

ABSTRACT

The sustained release drug delivery is the drug delivery system that achieves the release of drug in the proper amount at regular time interval over an extended period of time and is time independent. The aim of present work was to formulate and evaluate sustained release tablets of Paliperidone using natural gums in order to reduce the various side effects associated with Paliperidone as well as to overcome the manufacturing difficulties. For formulating sustained release drug delivery system, natural hydrophilic polymers are used. Natural binders provides the tablet formulations with good hardness and friability. These binders prolongs the dissolution rate of some slightly soluble drugs and can be chosen as good candidate for sustained release. Tablets were prepared by direct compression method using different drug-polymer concentration. FT-IR study revealed that there was no chemical interaction between the drug and polymers used. Pre-compression and post-compression parameters complied with Pharmacopoeial limit for the tablets. Four different gums (*Cassia roxburghii, Tamarindus indica , Azadirachta indica* and *Manihot esculenta*) were used in 3 different concentrations (35%, 50%, 75%) and was compared with the standard rate retardant polymer HPMC. The *in vitro* release study was performed and the results indicated that the formulation F12 (Neem gum 75%) was found to be the optimized formulation which can extend the release up to a period of 24 hours. The kinetic release data showed that the optimized formulation followed zero order kinetics. From the stability studies it was clear that the formulation was stable after 3 months at accelerated condition of $40^0C \pm 2^0C$/75% RH±5% in a stability chamber.

1. INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilised route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The popularity of this route may be due to its ease of administration and also due to the belief that by oral administration the drugs are well absorbed as the food stuffs that are ingested daily[1].

Among all the forms that are administered orally; solid oral dosage forms ie, tablets and capsules are the most preferred class of dosage forms. Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drugs or a mixture of drugs, with or without diluents. Depending on the mode of administration and the amount of medicinal substances, shape, size and weight of the formulations will get varied. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of tablet.

Recent advancement in the pharmaceutical field has resulted in the development of new technologies for drug delivery. The newly developed techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity, and/or targeting the delivery of drug to a tissue. The objectives in designing sustained or controlled delivery systems are:

- To reduce the frequency of the dosing.
- To increase effectiveness of the drug by localization at the site of action.
- Reducing the dose required or providing uniform drug delivery.
- To ensure safety and to improve efficacy of drugs as well as patient compliance.

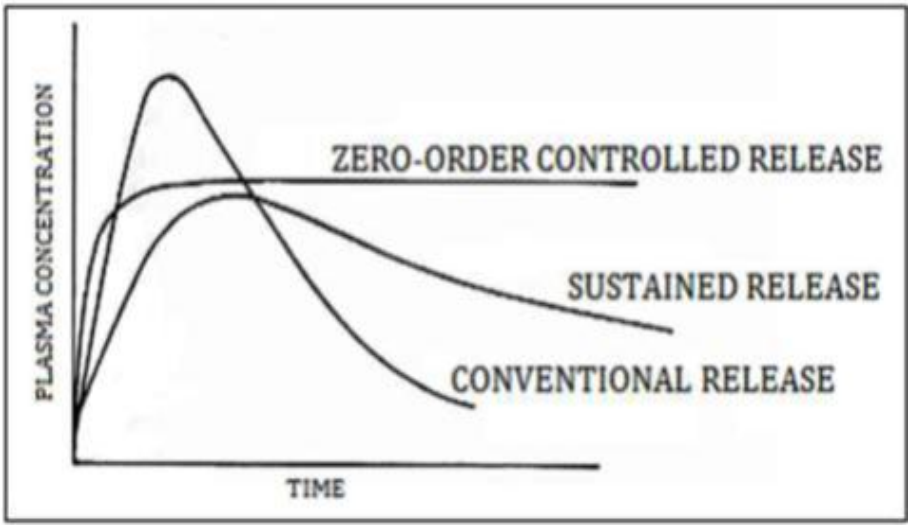


Fig 1: Plasma level concentration of CR, SR and conventional release.

Normally, hydrophilic polymers are preferred in formulating oral-controlled release tablets. When the dissolution medium penetrates in to the dosage form, the polymer material swells and by diffusion, the drug molecules comes out of the system at a determined rate by the nature, composition of polymer and type of formulation. The natural gums are selected since they are cheaper, bio-compactable and less toxic as compared to synthetic gums. Natural products are used as disintegrant, suspending agent, emulsifying agent and as binders used in formulating immediate and sustained release formulations.

The sustained release tablets are prepared by direct compression technique. HPMC, *Cassia roxburghii, Tamarindus indica, Azadirachta indica* and *Manihot esculenta* are the natural polymers used in various concentrations for formulating sustained release tablets.

Advantages of Conventional Oral Dosage Forms[2]

- ❖ High convenience.
- ❖ High level of patient acceptability.
- ❖ Good physical and chemical stability
- ❖ Convenience of self administration.
- ❖ Self administration can be done.
- ❖ Large scale production can be done easily.

- Easy to package and shipping.
- Sustained release products can be formulated by enteric coating.

Disadvantages of Conventional Oral Dosage Forms[2]

- Poor patient compliance.
- Fluctuation in blood level for small therapeutic index drugs.
- Chances for gastro intestinal irritant effects is high (Eg:- Aspirin)
- Difficult in administering to children, bed ridden and unconscious patients.
- Some drugs cannot be compressed into tablets.

Different Types of Tablets[1]

A) Oral Tablets for Ingestion

- Standard compressed tablets
- Multiple compressed tablets
  a. Layered tablets
  b. Compression coated tablets
  c. Inlay tablets
- Modified release tablets
- Delayed action tablets
- Targeted tablets
  a. Floating tablets
  b. Colon targeted tablets
- Chewable tablets

B) Tablets Used in the Oral Cavity

- Buccal tablets
- Sublingual tablets
- Troches and lozenges
- Dental cones

C) Tablets Administered by Other Routes

- Implantation tablets

- ❖ Vaginal tablets

D) Tablets Used to Prepare Solution

- ❖ Effervescent tablets
- ❖ Dispersible tablets
- ❖ Hypodermic tablets
- ❖ Tablet triturates

Sustained Release Drug Delivery System[2]

The sustained release drug delivery system is the drug delivery system that achieves the release of drug over an extended time period and is time independent. For formulating sustained release drug delivery system, hydrophilic polymers are used. An ideal system should deliver proper amount of drug at regular time interval at the site of action and should be in the therapeutic range.

Most preferred method for manufacturing sustained release drug delivery system is by direct compression method. Mostly hydrophilic polymers are used to formulate these tablets. The polymers used are HPMC, *Cassia roxburghii*, Tamarind powder, Neem powder and Tapioca starch. These polymers along with drug and other excipients are used in formulating an ideal sustained release formulation.

Table 1: Parameters for drug release and drug delivery[3]

PARAMETERS	PREFERRED VALUE
Molecular weight	< 1000
Solubility	> 0.1 µg /ml for pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability	From all GI segments
Release	Should not be influenced by pH and enzymes

Characteristics of Drug to be Used in Sustained Release Drug Delivery System[4,5]

- For shorter half-life drugs.
- For drugs that are absorbed throughout the GIT.
- For drugs having good solubility profile.
- For smaller dose drugs.

Advantages of Sustained Release Tablets[6]

- Avoid patient compliance.
- Low amount of drug is employed.
- Eliminate local or systemic side effects.
- Minimise drug accumulation.
- Economy.
- Improved efficiency in treatment.

Disadvantages of Sustained Release Tablets[6]

- Dose dumping.
- Limited choice of selecting desired dose in a unit dosage form.
- Poor *in vitro-in vivo* correlation.

Classification of Sustained Release Tablets[7]

Based on the mechanism of release of the drug from the polymer, the sustained release tablets are classified into

A) Diffusion controlled systems.

1) Matrix devices or systems.

a. Hydrophobic matrix system.
b. Hydrophilic matrix system.
c. Reservoir matrix system.
d. Semisolid matrix system.

2) Reservoir devices or systems.

B) Dissolution controlled systems.

1) Matrix dissolution controlled systems.

2) Encapsulation dissolution controlled systems.

3) Diffusion and dissolution controlled systems.

C) Osmotic controlled systems

1) Osmotic delivery systems for solids.

a) Type1: Single compartment

b) Type2: Multiple compartments

2) Osmotic delivery systems for liquids

D) Bio-degradable polymeric drug delivery system

1) Micro particles

2) Nano particles

3) Implants

DIFFUSION CONTROLLED RELEASE SYSTEMS

In diffusion controlled drug delivery system the dissolved drug diffuses through the polymeric barrier which act as the rate limiting membrane. In this the release rate does not follow zero order, as the path length for diffusion increases with time as the insoluble matrix gradually get depleted of drug diffusion of a drug molecule through a polymeric membrane. This is the basis of controlled drug delivery system. The diffusion controlled devices are formulated either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix.

In the case of reservoir type diffusion controlled devices, the rate of drug released (dm/dt) can be calculated by following equation

$$dm/dt = ADK\triangle C/l$$

where,

A	=	Area
D	=	Diffusion coefficient
K=		Partition coefficient of the drug between the drug core and the membrane
l	=	Diffusion path length
C	=	Concentration difference across the membrane

MATRIX DEVICES OR SYSTEMS

In this, drug is dispersed homogeneously in the matrix. The characteristics of matrix devices are:

1. Zero order release will not be obtained
2. Formulation is easy than reservoir devices
3. For higher molecular weight compounds, this system is used.

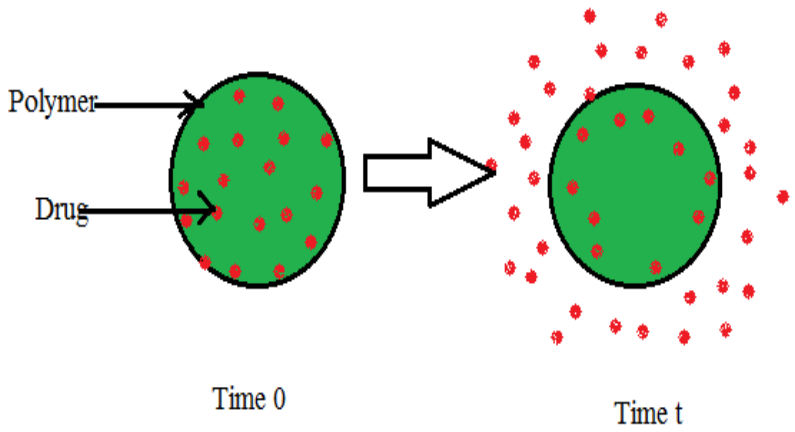


Fig.2 Schematic Representation of Diffusion Type Matrix System

RESERVOIR DEVICES OR SYSTEMS

In this, the drug core or reservoir is surrounded by a polymeric membrane which acts as the rate limiting barrier for the release of drug. The characteristics of the reservoir devices are:

1. Zero order release is obtained
2. The rate of release of the drug depends on the polymer used
3. Delivery of higher molecular weight compounds is difficult.

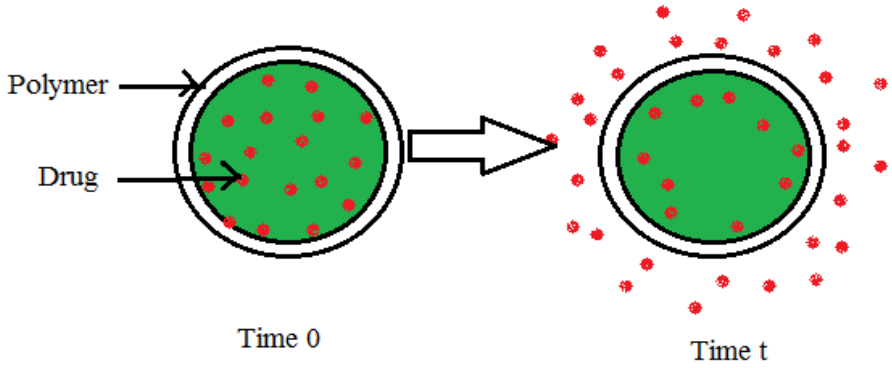


Fig.3: Schematic Representation of Diffusion Type Reservoir System

DISSOLUTION CONTROLLED RELEASE SYSTEMS

These are comparatively easy to formulate. The drugs used in this system will have slow dissolution rate (Griseofulvin and Digoxin). Drugs with high aqueous solubility and dissolution rate cannot be used for this type of drug delivery. Dissolution controlled release systems can be formulated by incorporating the drug in an insoluble polymer and coating the drug particle with polymeric material of varying thickness. This is done in order to control the release of the drug in the gastro-intestinal medium. The diffusion across the aqueous boundary layer acts as the rate limiting step.

The rate of dissolution (dm/dt) can be found out by:

$$dm/dt = ADS/h$$

S = Aqueous solubility of drug

A = Surface area of tablet

D = Diffusivity of drug

H = Thickness of boundary layer.

MATRIX DISSOLUTION CONTROLLED SYSTEMS

In this, bees wax, carnauba wax are used which determines the drug release rate by controlling the rate of penetration of fluid into the matrix. The drug release from these systems is based on first order kinetics.

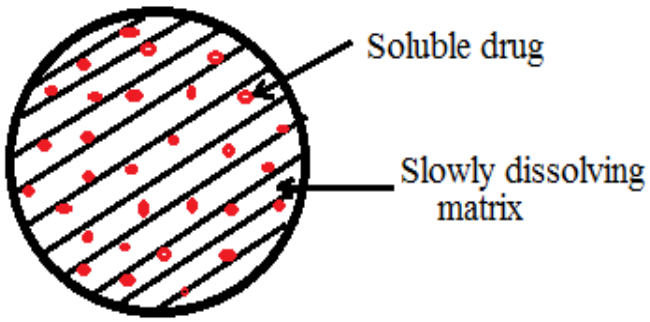


Fig.4: Schematic Representation of Dissolution type Matrix System

RESERVOIR DISSOLUTION CONTROLLED SYSTEMS

In this, the drug particles are encapsulated by different micro encapsulation techniques with poly ethylene glycol and cellulose. The dissolution rate depends on solubility of coat and thickness of coating.

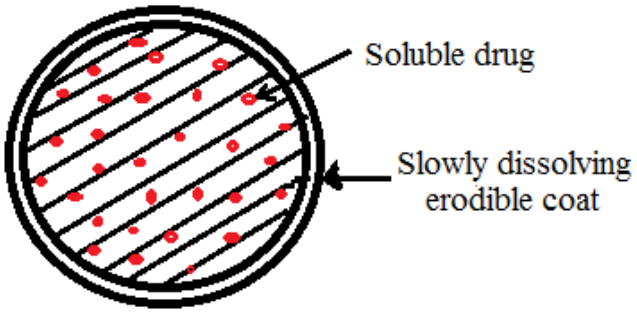


Fig 5: Schematic Representation of Dissolution type Reservoir System

OSMOTIC CONTROLLED SYSTEMS

The osmotic drug delivery is useful for poorly soluble drug, pulsative drug release and zero order release. The different techniques used for the formulation of osmotic drug delivery system include push-pull osmotic pump, osmotic bursting osmotic pump, liquid oral osmotic system, sandwiched osmotic tablets etc. In these systems, the controlled delivery of drug is due to the change in osmotic pressure. The delivery of drug in the system is independent of the physiological factors in the gastrointestinal tract. Factors that affect the release of the drug are solubility and osmotic pressure of the core, size of the delivery orifice and nature of the rate controlling membrane.

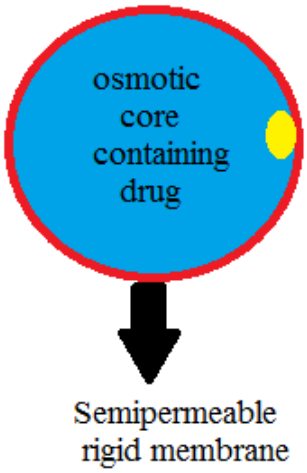


Fig. 6: Type-A osmotic system

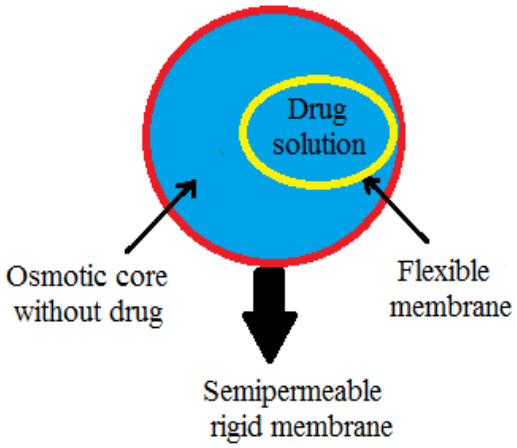


Fig.7: Type-B osmotic system

BIODEGRADABLE POLYMERIC DRUG DELIVERY SYSTEM

Nanoparticles made from solid lipids are attracting increasing attention as colloidal drug carriers for iv application. The nanoparticles range as 50-1000nm and they are composed of physiological lipids. These particles are in solid state at room temperature, so the mobility of incorporated drugs is reduced. They are stabilized with non-toxic surfactants like polaxamer and lecithin. Due to the production by high pressure homogenization they can be produced on large industrial scale. In addition, this production method avoids the use of organic solvents. Compared to traditional carriers the SLN have compared advantages of polymeric nanoparticles and o/w fat emulsions for parenteral administration. There are several studies are conducted for the optimization of production parameters, long term stability, recrystallisation behaviour, morphological characterization and in -vivo toxicity have been undertaken. A basic problem in early work with lipid particles in the nanometre range was the generally observed burst release of drugs; a prolonged release could not be achieved. The aim of the investigation was therefore, to assess if a prolonged release is basically possible.

POLYMERS USED IN SUSTAINED RELEASE TABLETS[8,9]

Sustained release drug delivery means not only prolonged duration of drug delivery but also implies predictability and reproducibility of drug release kinetics. The polymers used for the sustained release drug delivery should retard the release of drug. Usually natural acrylic and cellulose polymers have been used for formulating sustained release formulations. Now a day, microencapsulation is selected for designing sustained release formulations where thin coatings are applied to small particles of solids or liquids. Microencapsulation by natural products such as starch, proteins, waxes are also done.

HPMC, chitosan and sodium alginate are the most preferable polymers as they are non-toxic, biocompatible, and biodegradable and can be easily modified by physical and chemical means. Methyl cellulose has long chain substituted polymers which is used as binding, disintegrating and suspending agent where as sodium carboxy methyl cellulose is a salt of poly carboxy methyl ether of cellulose which is used as coating, binding, stabilising and suspending agent. Poly vinyl pyrrolidone

(PVP) is 1-ethenyl-2-pyrrolidonone homo polymer which is used as disintegrant, dissolution aid, suspending agent and tablet binder.

Now a days, natural binders are also used widely for formulating sustained release tablets as they are less toxic, biodegradable, easily available and low cost. Different natural agents like starches, gums, mucilage have binding, disintegrating, and filler activities. Different starches like rice, potato, tapioca and seeds of *Cassia roxburghii* and tamarind seed powder and gums like okra gum, neem gum, olibanum gum etc are used for formulating sustained release formulations.

The *Cassia roxburghii* seeds are collected and its size is get reduced by hammer milling and is powdered. This is soaked in water for one day and is extracted by filtration. The gum is get separated by centrifugation and it is dried. The gum at different concentration is used for formulating the sustained release tablets.

The tamarind seeds are collected from the tamarind tree and are heated with sand for some time. This is done to remove the outer coating of the seed and it is hammer milled for size reduction of the seed. Then it is grinded and is passed through sieve number 100.

The tapioca tubers are collected and are peeled, washed and cut into small pieces. Then it is soaked in water for one hour. The whole mass is milled in to fine powder and is dried and is sieved using sieve number 100.

The neem exudate is collected from the bark, it is hydrated in distilled water. Extraneous material was removed, dried and powdered. It is passed through sieve number 100.

MECHANISM OF DRUG RELEASE FROM THE TABLET[10,11,12]

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving towards the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

Derivation of the mathematical model to describe this system involves the following assumptions:

A pseudo-steady state is maintained during drug release,

The diameter of the drug particles is less than the average distance of drug diffusion through the matrix,

The bathing solution provides sink conditions at all times.

The release behaviour for the system can be mathematically described by the following equation:

$$dM/dh = Co.\ dh - Cs/2$$

Where,

dM = Change in the amount of drug released per unit area.

dh = Change in the thickness of the zone of matrix that has been depleted of drug.

Co = Total amount of drug in a unit volume of matrix.

Cs = Saturated concentration of the drug within the matrix.

Additionally, according to diffusion theory:

$$dM = (Dm.\ Cs / h)\ dt$$

Where,

Dm = Diffusion coefficient in the matrix.

h = Thickness of the drug-depleted matrix.

dt = Change in time.

By combining equation 1 and equation 2 and integrating:

$$M = [Cs.\ Dm\ (2Co - Cs)\ t]\ ½$$

When the amount of drug is in excess of the saturation concentration then:

$$M = [2Cs.Dm.Co.t]\ 1/2$$

Equation 3 and equation 4 relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores.

The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix:

$$M = [Ds.\ Ca.\ p/T.\ (2Co - p.Ca)\ t]\ 1/2$$

Where,

p	=	Porosity of the matrix.
t	=	Tortuosity.
Ca	=	solubility of the drug in the release medium.
Ds	=	Diffusion coefficient in the release medium.
T	=	Diffusional path length.

For pseudo steady state, the equation can be written as:

$$M = [2D.Ca\ .Co\ (p/T)\ t]\ ½$$

The total porosity of the matrix can be calculated with the following equation:

$$p = pa + Ca/\ \rho + Cex\ /\ \rho ex$$

Where,

p	=	Porosity.
ρ	=	Drug density.
pa	=	Porosity due to air pockets in the matrix.
ρex	=	Density of the water soluble excipients.
Cex	=	Concentration of water soluble excipients.

For the purpose of data treatment, equation 7 can be reduced to:

$$M = k.\ t\ 1/2$$

Where, **k** is a constant, so that the amount of drug released versus the square root of time will be linear, if the release of drug from matrix is diffusion-controlled. If this is the case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters:

- Initial concentration of drug in the matrix.
- Porosity.
- Tortuosity.
- Polymer system forming the matrix.

2. REVIEW OF LITERATURE

Singh AK *et al*[13], prepared matrix tablets of aceclofenac by direct compression process using natural gums (xantham gum and karaya gum) in different ratios. The effect of natural gums on the release profile of drug from matrix system for once daily sustained release tablets formulations were evaluated. The *in-vitro* release of drug was performed in phosphate buffer of pH 7.4 for 24 hours. . The tablets with FXK resulted in more uniform controlled drug release matrices than FX and FK formulations. . Xantham gum matrices showed good sustained effect on the release of aceclofenac than FK alone matrices. The FXK formulation was found to provide the required release rate, with zero-order release kinetics. It is cost effective and more similar to reference standard.

S.Jaganath *et al*[14], prepared and evaluated silymarin controlled release tablets using natural gum polymers like xantham gum and guar gum in the drug polymer ratio of 1:0.25, 1:0.5 and 1:0.75. The *in vitro* release study was performed using 900ml of phosphate buffer of pH7.4 for 10 hours using USP type II dissolution apparatus. The *in vitro* drug release of silymarin from the formulation without polymer was found to be 99% in 3.5 hours. When the polymer ratio was increased, the percentage drug release of silymarin was decreased. The silymarin, xantham gum combination in the ratio of 1:0.75 showed the in vitro drug release of 73.92%, thus sufficiently sustaining the release of drug.

Azharuddin *et al*[15], prepared and evaluated controlled release matrix tablets of losartan potassium by direct compression using natural polymer like xantham gum and synthetic hydrophilic polymer like HPMC. Results of this study confirmed that the polymer concentration plays a major role in drug release. It was observed that with increasing concentration of the polymer, the percentage of drug release was decreased.

Roohullah *et al*[16], prepared and evaluated various formulations of sustained-release matrix tablets of carbamazepine. The matrix tablets were prepared by solvent evaporation method using hydroxypropyl methyl cellulose (HPMC), carboxy methyl cellulose (CMC) and polyvinylpyrrolidon-K90 (PVP-K90) as release sustaining

materials. Formulations were designed to develop twice daily sustained release dosage form. . HPMC based matrix tablets with the drug to polymer ratio of 1:2 was found to sustain the release of the carbamazepine up to 12 hours, while CMC and PVP-K90 with drug to polymer 1:2 ratio was able to control the drug release up to 8 and 6 hours respectively. The stability study also confirmed that the drug is stable in HPMC based matrix tablets. So HPMC was selected as the best polymer to formulate the sustained release formulation of carbamazepine for 12 hours.

Asaduzzaman *et al*[17], designed and evaluated oral sustained release matrix tablets of ranolazine by wet granulation using Methocel K4M CR as the retardant polymer. *In vitro* release studies were performed using USP type II apparatus (paddle method) in 900 ml of 0.1N hydrochloric acid at 50 rpm for 8 hours. Based on the dissolution data comparison with the standard, F-5 formulation (16% Methocel K4M CR $^{w}/_{w}$ of drug) was elected as the best formulation. They concluded that the oral sustained release tablets of ranolazine provided a better option for development of a twice daily formulation of the drug.

Emeje *et al*[18], prepared oral sustained release matrix tablets of zidovudine (ZDV) using different types, proportions and blends of carbopol 71G (C71) and a plant gum obtained from *Abelmoschus esculentus* (AEG). The effect of various formulation factors like polymer proportion, polymer type and pH of the dissolution medium on the *in vitro* release of the drug was studied, using the half change technique, in 900 ml of dissolution medium, at 100 rpm. The results of drug dissolution studies showed improved drug release retardation effects of the polymer blends. Blending a natural gum with a synthetic polymer could achieve equivalent or better performance while being more economical.

Raghavendra Rao *et al*[19], formulated and evaluated sustained release matrix tablets of water soluble tramadol hydrochloride using different polymers like hydroxy propyl methyl cellulose (HPMC) and natural gums like karaya gum (KG) and carrageenan (CG). The *in vitro* release study was performed in 0.1 N hydrochloric acid of pH 1.2 for 2 hours and in phosphate buffer of pH 6.8 up to 12 hours. The effect of polymer concentration and polymer blend concentration were studied. It was observed that matrix tablets that contained polymer blend of HPMC/CG successfully

sustained the release of drug upto 12 hours. Among all the formulations, formulation F16 which contained 20% HPMC K15M and 80% of CG released the drug which followed zero order kinetics by swelling, diffusion and erosion and the release profile of formulation F16 was comparable with the marketed product. Stability studies (40±2ºC/75±5%RH) for 3 months indicated that tramadol hydrochloride was stable in the matrix tablets.

Mughal *et al*[20], developed propranolol hydrochloride-loaded matrix tablets using guar gum, xantham gum, and hydroxypropyl methylcellulose (HPMC). Tablets were prepared by wet granulation using these polymers alone and in combination, and physical properties of the granules and tablets were studied. Drug release was evaluated in simulated gastric and intestinal media. It was concluded that these polymers can be used to formulate successful sustained release propranolol hydrochloride matrix tablets that have desirable characteristics.

Basavaraj *et al*[21], developed and evaluated sustained release formulation of aceclofenac based on monolithic matrix technology. The tamarind seed polysaccharide (TSP) was extracted from tamarind kernel powder and this polysaccharide was utilized in the formulation of matrix tablets containing aceclofenac by wet granulation technique and evaluated for its drug release characteristics. Formulation was optimized on the basis of acceptable tablet properties like hardness, friability, drug content and weight variations. The *in vitro* drug release and stability studies were also conducted. The results indicated that a decrease in release kinetics of the drug was observed by increasing the polymer concentration. They concluded that the matrix tablets were found to be effective in sustaining the drug release up to 12 hours.

Afrasim *et al*[22], formulated of sustained release matrix tablets of diltiazem hydrochloride (DTZ) using cross-linked karaya gum [modified karaya gum (MK)]. Modified karaya gum (MK) was prepared by cross-linking karaya gum with tri-sodium tri-metaphosphate (STMP) which was used as a cross linker. Matrix tablets of DTZ were prepared using varying ratios of unmodified karaya gum (K) and MK by direct compression. Drug release was by water uptake, diffusion and erosion mechanisms. Tablets formulated with MK showed higher mean dissolution time

(MDT) and lower dissolution efficiency than those prepared with karaya gum. Drug release for tablets prepared with pure K was 99.9 % at the end of 10 hours while the tablet made with MK was 68.2 % at the end of 12 hours. MK sufficiently controlled the drug release unlike K which exhibited rapid drug release efficiency. The results of the study showed that modified karaya gum is a potential matrix material for formulating suitable sustained-release matrix tablets of diltiazem.

Saha *et al*[23], developed oral controlled release matrix tablet formulations of isoniazid using hydroxypropyl methylcellulose (HPMC) as a hydrophilic release retardant polymer and studied the influence of various formulation factors like proportion of the polymer, polymer viscosity grade, compression force, and release media on the *in vitro* release characteristics of the drug. The formulations were developed using wet granulation technology. They concluded that the hydrophilic polymer like HPMC could be used as a matrix material to design controlled release formulations of a water-soluble drug isoniazid with desired quality and release characteristics.

S. Brito Raj *et al*[24], prepared bilayer tablet of metformin hydrochloride (SR) with metoprolol tartarate (IR) as a once daily formulation. The formulations of tablets were prepared by using release retarding agents like HPMC K100, Eudragit S 100 for sustained release (SR) layer and super disintegrants like crosspovidone, sodium starch glycolate (SSG) for immediate release (IR) layer. Both sustained and immediate release granules were evaluated for flow property. Bilayer tablets were evaluated for weight variation, hardness, thickness, swelling index and *in-vitro* drug release for 12 hours. All the formulations obey zero order release kinetics and the mechanism of drug release was found to be non fickian diffusion by fitting the data to peppas equation. The results suggested that the developed bilayer tablet of metformin hydrochloride (SR) with metoprolol tartarate (IR) could perform therapeutically better and improved efficacy than conventional dosage forms.

Jekku *et al*[25], designed and characterized sustained release matrix tablets of glimepiride by using synthetic and natural polymers. Sustained release tablets of glimepiride was prepared by wet granulation method using various concentrations of synthetic polymers (HPMC K 15M & HPMC K 4M) and natural polymers (starch

acetate & starch urea). The study revealed that the various concentrations of natural polymers (starch acetate & starch urea) sustained the drug release when compared to synthetic polymers (HPMC K 15M & HPMC K 4M). Among all the formulations F-12 formulation with starch urea at the concentration of 30% was found to have more sustained action when compared to other formulations with the same concentration of other polymers and it showed drug release of 49.70 % at the end of 7hours.

Deepthi Kodam *et al*[26], formulated and evaluated sustained release matrix tablets of tramadol hydrochloride using different hydrophilic and hydrophobic polymers like hydroxyl propyl methylcellulose, polyethylene oxide, ethyl cellulose and eudragit. All the batches were evaluated for angle of repose, Carr's index, Hausner ratio, hardness, thickness, weight variation, drug content and *in-vitro* release characteristics. The optimized tablets having HPMC provided more sustained drug release than other polymers. FTIR studies indicated that there was no interaction between the drug and excipients and stability studies had proved the integrity of the developed matrix tablets.

Arul Kumaran KSG *et al*[9], formulated and evaluated tablets of paracetamol and diclofenac sodium using *Cassia roxburghii* seed gum powder as binder. The study revealed that *Cassia roxburghii* seed gum powder is a better binder for preparing tablet since it minimized the capping tendency without adversely affecting other crucial properties of the tablet. *Cassia roxburghii* gum produced tablets with longer disintegration time and longer dissolution time than tablets with standard starch binder.

Habeeb MD *et al*[27], developed sustained release bilayer tablets of water soluble drug tramadol hydrochloride using guar gum, HPMC, NaCMC and xantham gum, either alone or in combinations. Tablets were prepared by direct compression for immediate release and wet granulation method for sustained release and evaluated for various physical parameters. The drug release studies were performed using USP apparatus type I using 0.1N hydrochloric acid and phosphate buffer of pH 6.8 as dissolution medium. The drug release was dependent on the type and concentration of the polymer. Drug release was faster from tablets prepared with guar gum, NaCMC and HPMC alone. However, in combination with HPMC, NaCMC, guar gum with

xantham gum it sustained drug release effectively. All the formulations followed zero order release mechanism. Higuchi plots for all the formulations were linear indicating the drug release by diffusion controlled. Hixon-Crowell cube root model showed high r^2 value proportionality due to erosion of hydrophilic gel layer. To explore the release pattern, results of the *in-vitro* dissolution data were fitted to the Korsmeyer-Peppas equation, which characterizes the transport mechanism indicates the non fickian transport it refer to combination of both diffusion and erosion rate release.

T. Sivakumar *et al*[28], formulated and characterised controlled release tablets containing the natural gum obtained from *Mangifera indica.* The dissolution study of the tablet revealed that the formulation containing $5\%^{w}/_{w}$ of the gum performed as a better binding agent than the standard binder gum acacia at the same concentration. The study also revealed that *Mangifera indica* gum is pH sensitive and therefore it can be used in the formulation of intestinal drug delivery systems.

Jaleh Varshosaz *et al*[29], developed matrix sustained release tablets of highly water-soluble tramadol hydrochloride using natural gums like xantham gum (X gum) and guar gum (G gum) and hydrophilic matrices like hydroxypropyl methylcellulose [HPMC] or carboxymethyl cellulose [CMC]. Matrix tablets were prepared by direct compression method. Different ratios of 100:0, 80:20, 60:40, 20:80, 0:100 of G gum (or X): HPMC, X gum:G gum, and triple mixture of these polymers (G gum, X gum, HPMC) were applied. After evaluation of physical characteristics of tablets, the dissolution test was performed in the phosphate buffer media of pH 7.4 for 8 hours. Guar gum alone cannot efficiently control drug release, and X gum has higher drug retarding ability than G gum. The combination of each natural gum with HPMC leads to a greater retarding effect compared with a mixture of two natural gums.

Amit S Yadav *et al*[30], prepared oral controlled release zidovudine matrix tablets by using guar gum as rate controlling polymer and to evaluate drug release parameters as per various release kinetic models. The tablets were prepared by wet granulation method. Granules were prepared and evaluated for loose bulk density, tapped density, compressibility index and angle of repose and the tablets exhibited satisfactory results. The *in-vitro* dissolution study was carried out for 12 hours using paddle (USP type II) method in phosphate buffer of pH 6.8 as the dissolution medium. Among all

the formulations, the formulation with 15% of guar gum shows 95.97% of drug release at the end of 12 hours. Selected formulation was subjected to stability studies for 3 months, which showed stability with respect to release pattern. Fitting the *in-vitro* drug release data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release.

Sajid Ali *et al*[31], prepared and evaluated sustained release matrix tablets of phenytoin sodium using natural polymers. The tablets were prepared by the wet granulation method using water as granulating agent along with matrix materials like guar gum, sodium alginate, tragacanth and xantham gum with varying percentage. The mechanism of drug release was diffusion coupled with erosion. Guar gum alone could not control the phenytoin release effectively for 12 hours. It was evident from the results that matrix tablet formulated using 55% guar gum with 10% gum acacia with water as granulating agent was the best formulation for the sustained release matrix tablets of phenytoin.

3. AIM AND OBJECTIVE

AIM

The aim of this investigation is to formulate and evaluate paliperidone sustained release tablets using natural polymers and to compare with standard rate retardant polymer HPMC.

GENERAL OBJECTIVE

To estimate the binding capacity of various natural gums in granules and tablet formulations as a release retardant.

SPECIFIC OBJECTIVES

- To collect and isolate gums from different natural sources.
- To prepare granules by direct compression method and determine their physical properties.
- To optimise the binder concentration using appropriate experimental design.
- To prepare and compress tablets of the optimum formulation and compare with standard rate retardant polymer, HPMC.
- To evaluate the *in vitro* release principle of sustained release paliperidone tablets and evaluate the release mechanism on the behalf of various kinetic modules.
- To perform the stability study on optimised paliperidone formulation.

4. PLAN OF WORK

1. Review of literature
2. Collection and isolation of the gums from different natural sources
3. Preformulation studies
    - Bulk density
    - Tapped density
    - Carr's index
    - Hausner's ratio
    - Angle of repose
4. Preparation of tablet by direct compression method
5. Post formulation studies
    - Hardness
    - Friability
    - Weight variation
    - Content uniformity
    - Assay
    - Dissolution studies
6. Kinetic analysis
    - First order
    - Zero order
    - Higuchi order
7. Stability studies

5. DRUG PROFILE[32,33,34,35]

Paliperidone also known as **9-hydroxyrisperidone**, is an atypical antipsychotic developed by Janssen Pharmaceutica. Chemically, paliperidone is the primary active metabolite of the older atypical antipsychotic risperidone. Paliperidone is 9-hydroxyrisperidone, i.e. risperidone with an extra hydroxyl group). It is indicated for the acute and maintenance treatment of schizophrenia

❖ **IUPAC:**

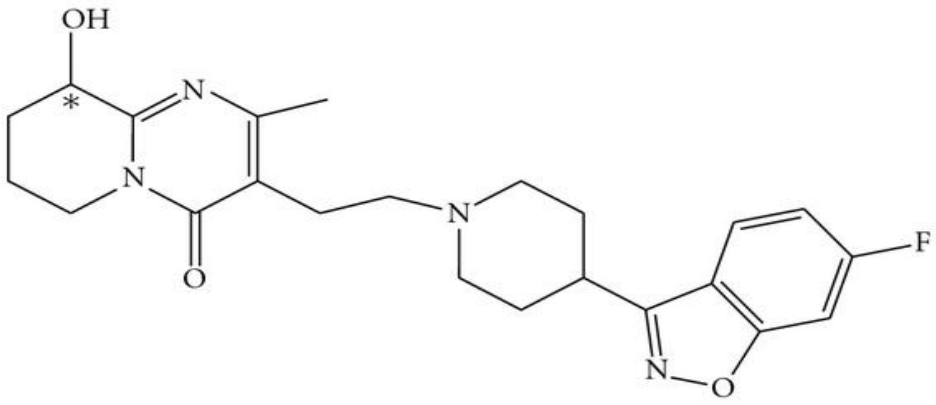
(*RS*)-3-[2-[4-(6-fluorobenzo[*d*]isoxazol-3-yl)-1-piperidyl] ethyl] 7-hydroxy -4 -methyl-1, 5-diazabicyclo[4.4.0]deca-3,5-dien-2-one.

❖ **Molecular formula:**

$C_{23}H_{27}FN_4O_3$

❖ **Molecular Structure:**

Chemical structure of paliperidone.



* indicates position of chiral carbon atom.

❖ **Mol. mass:**

426.484 g/mol

❖ **Bioavailability:**

28% (oral)

❖ **Half-life:**

23 hours (oral)

❖ **Solubility:**

Paliperidone is sparingly soluble in 0.1N HCl and methylene chloride; practically insoluble in water, 0.1N NaOH, hexane; and slightly soluble in N, N-dimethylformamide.

❖ **Pharmacology:**

The exact mechanism of action of paliperidone is unknown; it is believed that the action of paliperidone and respiridone are similar, if not in identical pathways. Therapeutic effect may be due to a combination of D2 and 5-HT2A receptor antagonism. Paliperidone also has antagonist effect at α1 and α2 adrenergic receptors and at H1 histamine receptors. It does not bind to muscarinic acetylcholine receptors.

❖ **Dose:**

Extended-release tablets 3 mg, 6 mg , 9 mg and 12 mg.

❖ **Side Effects and Adverse Reactions**

- The common side effects of paliperidone are restlessness and extrapyramidal disorder, including involuntary movements, tremors and muscle stiffness. There may be chances for sexual dysfunction while administering this drug in combination with SSRIs.
- Neuroleptic malignant syndrome is a rare, but potentially lethal reaction to the medication. Heart rhythm changes potentially serious may make paliperidone risky for people with some heart conditions.
- Tardive dyskinesia, is permanent side effect reported with paliperidone and other neuroleptics. The risk of tardive dyskinesia increases with total dose and thus becomes more likely the longer a person takes paliperidone.
- High blood sugar, hyperprolactinemia or elevated levels of the hormone prolactin, potentially leading to the absence of a menstrual period,

breasts producing milk, the development of breasts by males and erectile dysfunction are also seen.

- Complications associated with pre-existing narrowing or blockage of the gastrointestinal tract (esophagus, stomach or small or large intestine).
- Fainting or light-headedness when standing up or sitting up too quickly.
- Risk in people with a seizure disorder or a history or health conditions that make seizures.
- Caution should be exercised before prescribing paliperidone to pregnant or nursing women.
- Associated with decreases in the counts of white cells in circulating blood.

6. DISEASE PROFILE[36]

Schizophrenia is a brain disorder that distorts the way a person thinks, acts, expresses emotions, perceives reality and relates to others. Depression is an illness that is marked by feelings of sadness, worthlessness or hopelessness, as well as problems concentrating and remembering details. Bipolar disorder is characterized by cycling mood changes, including severe highs (mania) and lows (depression).

Schizoaffective disorder is a life-long illness that can impact all areas of daily living, including work or school, social contacts and relationships. Most people with this illness have periodic episodes, called relapses, when their symptoms surface. While there is no cure for schizoaffective disorder, symptoms often can be controlled with proper treatment.

- **Symptoms of Schizoaffective Disorder**

A person with schizoaffective disorder has severe changes in mood and some of the psychotic symptoms of schizophrenia, such as hallucinations, delusions and disorganized thinking. Psychotic symptoms reflect the person's inability to tell what is real from what is imagined. Symptoms of schizoaffective disorder may vary greatly from one person to the next and may be mild or severe. Symptoms of schizoaffective disorder may include:

- **Depression**

  - Poor appetite
  - Weight loss or gain
  - Changes in sleeping patterns (sleeping very little or a lot)
  - Agitation (excessive restlessness)
  - Lack of energy
  - Loss of interest in usual activities
  - Feelings of worthlessness or hopelessness
  - Guilt or self-blame
  - Inability to think or concentrate
  - Thoughts of death or suicide

❖ **Mania**

- Increased activity, including work, social and sexual activity
- Increased and/or rapid talking
- Rapid or racing thoughts
- Little need for sleep
- Agitation
- Inflated self-esteem
- Distractibility
- Self-destructive or dangerous behavior (such as going on spending sprees, driving recklessly or having unsafe sex)

❖ **Schizophrenia**

- Delusions (strange beliefs that are not based in reality and that the person refuses to give up, even when presented with factual information)
- Hallucinations (the perception of sensations that aren't real, such as hearing voices)
- Disorganized thinking
- Odd or unusual behaviour
- Slow movements or total immobility
- Lack of emotion in facial expression and speech

➢ **Causes of Schizoaffective Disorder**

While the exact cause of schizoaffective disorder is not known, researchers believe that genetic, biochemical and environmental factors are involved.

- **Genetics (heredity):** A tendency to develop schizoaffective disorder may be passed on from parents to their children.
- **Brain chemistry:** People with schizophrenia and mood disorders may have an imbalance of certain chemicals in the brain. These chemicals, called neurotransmitters, are substances that help nerve cells in the brain send messages to each other. An imbalance in these

chemicals can interfere with the transmission of messages, leading to symptoms.

- **Environmental factors:** such as a viral infection, poor social interactions or highly stressful situations -- may trigger schizoaffective disorder in people who have inherited a tendency to develop the disorder.

7. POLYMER PROFILE[37]

HYDROXY PROPYL METHYL CELLULOSE

Non-proprietary Names :

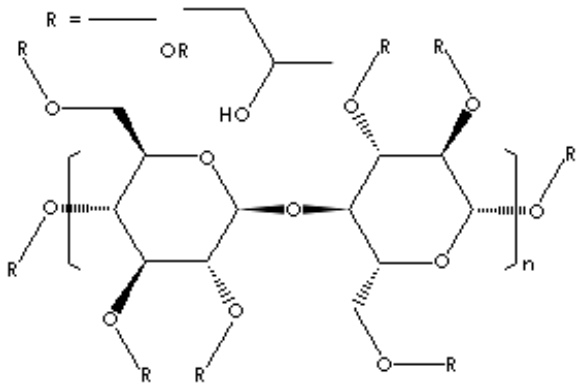
BP	**:**	Hypromellose
JP	**:**	Hypromellose
PhEur	**:**	Hypromellose
USP	**:**	Hypromellose

Synonyms:

Benecel MHPC, E464, hypromellosum; Methocel; methylcellulose propylene glycol ether; methyl hydroxylpropyl cellulose; Metolose; MHPC; Pharmacoat; Tylopur; Tylose MO.

Chemical Name **:** Cellulose hydroxypropyl methyl ether

Structural Formula:



Where R is H, CH3, or CH3CH (OH) CH2

Descriptions:

Hypromellose is an odorless and tasteless, white or creamy white fibrous or granular powder.

Typical Properties:

Acidity/alkalinity	**:**	pH = 5.5–8.0 for a 1% w/w aqueous solution.
Ash	**:**	1.5–3.0%

Autoignition temperature	**:**	360ºC
Density (bulk)	**:**	0.341 g/cm^3
Density (tapped)	**:**	0.557 g/cm^3
Density (true)	**:**	1.326 g/cm^3
Melting point	**:**	browns at 190–208ºC; chars at 225–238ºC.
Glass transition temperature	**:**	170–180ºC.
Loss on drying	**:**	< 10.0%
Residue on ignition	**:**	1.0%

Maximum Limits of Impurities:

Arsenic <3PPM

Heavy metals <0.001%

Methoxy (Percent) 23.2

Hydroxy propoxy (Percent) 8.5

Moisture content

Hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.

Solubility

Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol.

Specific gravity **:** 1.26

Functional Category

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

Pharmaceutical Applications

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets.

CASSIA ROXBURGHII GUM

Synonym	**:**	Ceylon Senna, Red Cassia, Horse Cassia
Source	**:**	It is the gum obtained from the seeds of Cassia roxburghii
Family	**:**	Fabaceae/Leguminosae

Physicochemical Properties:

pH	**:**	6.5
Viscosity	**:**	.876 poise
Bulk Density	**:**	0.69g/ml
Tappped Density	**:**	0.81g/ml
Angle of Repose	**:**	37.56º
Carr's Index	**:**	14.81%
Swelling Ratio	**:**	6.2
Hausner's Ratio	**:**	1.17
Solubility	**:**	Dissolves in warm water forming a colloidal solution swells in cold water insoluble in organic solvents
Stability	**:**	The gum is normally stable at moderate temperature and pressure.
Storage	**:**	Stored in a cool, dry place
Pharmaceutical Applications	**:**	The gum is used in slow release formulations. It is used especially when high mechanical strength is needed.

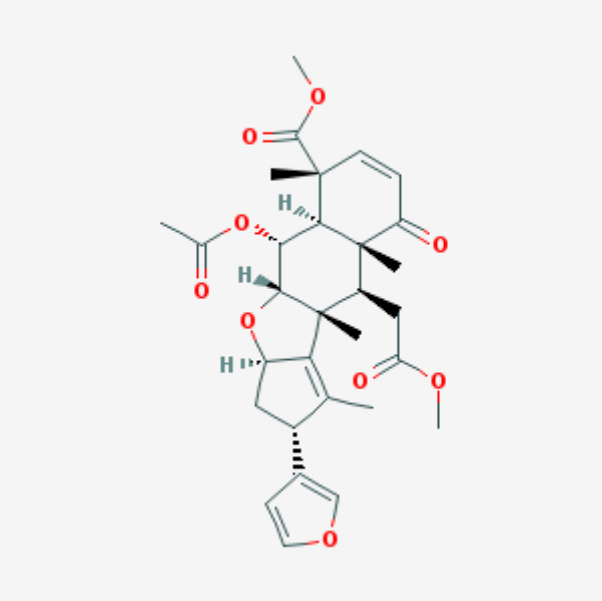
NEEM GUM

Synonym : Indian lilac, Margosa

Source : It is a typical plant gum exudated from the tree *Azadirachta indica*.

Family : Meliaceae

Chemical Constituents : Nimbin, Nimbinin, Nimbosterol, Mannose, Glucosamine, Arabinose, Galactose, Fructose, Xylose and Glucose



Structure of Nimbin

Physicochemical Properties:

pH : 6.7±0.5

Viscosity : 1.1032 poise

Bulk Density : 0.611g/ml

Tappped Density : 0.710g/ml

Angle of Repose : 28.711º

Carr's Index	**:**	12.983%
Solubility	**:**	Very soluble in warm water Partially soluble in cool water.
Stability	**:**	The gum is normally stable at moderate temperature and pressure.
Storage	**:**	Stored in a tightly closed container.
Pharmaceutical Applications	**:**	The neem gum is used as binding agent, suspending agent and transdermal film forming agent.

TAMARIND GUM

Source	**:**	Tamarind gum is obtained from the endosperm of seeds of the tamarind tree, *Tamarindus indica.*
Family	**:**	Leguminoseae
Chemical Constituents	**:**	Tamarind seed gum, a crude extract of tamarind seeds, is rich in polysaccharide, which contains glucose, xylose and galactose units, in a molecular ratio of 3:2:1

Physicochemical Properties:

pH	**:**	6.81±0.21
Viscosity	**:**	0.8928 poise
Moisture Content	**:**	10.78%
Ash Content	**:**	0.39%
Swelling Index	**:**	1700.56%
Water Retention	**:**	20.34%
True Density	**:**	1.015g/ml
Bulk Density	**:**	0.651g/ml
Tappped Density	**:**	0.781g/ml
Angle of Repose	**:**	29.51º
Carr's Index	**:**	16.64%
Solubility	**:**	Quickly soluble in warm water forming a

viscous colloidal solution sparingly soluble in cold water insoluble in ethanol, methanol, acetone and ether

Stability **:** The gum is stable at temperature less than 30ºC

Storage **:** Stored in a well closed container.

Pharmaceutical Applications **:** The tamarind gum is used as binding agent, emulsifier, suspending agent, sustaining agent. It is also used to improve dissolution, to prolong nasal mucoadhesion.

TAPIOCA STARCH

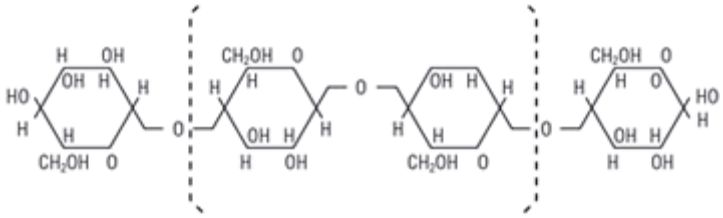
Synonym	**:**	Manioc, Yuca, Mogo, Mandioca
Source	**:**	Tapioca starch is obtained from the tuberous root of the tapioca plant, *Manihot esculenta*
Family	**:**	Euphorbiaceae
Chemical Constituents	**:**	Reducing sugar, Non-reducing sugar, Protein and Fibre

Physicochemical Properties:

pH	**:**	6.56
Viscosity	**:**	.987 poise
Moisture Content	**:**	10-13%
Ash Content	**:**	0.4%
Bulk Density	**:**	0.714g/ml
Tappped Density	**:**	0.892g/ml
Angle of Repose	**:**	31.28º
Carr's Index	**:**	14.49%
Solubility	**:**	Quickly soluble in warm water.
Stability	**:**	The gum is normally stable at moderate temperature and pressure.
Storage	**:**	Stored in a tightly closed container
Pharmaceutical Applications	**:**	It is widely used in pharmaceuticals, primarily as a binder/ diluents.

MICROCRYSTALLINE CELLULOSE

Structural formula:



Non-proprietary name:

- BP **:** Microcrystalline cellulose
- JP **:** Microcrystalline cellulose
- PhEur **:** Cellulosum microcrystallinum
- USPNF **:** Microcrystalline cellulose

Synonym	**:**	Avicel; Cellulose gel; tabulose Crystalline cellulose; E460; Emcocel Fibrocel; vivacel
Chemical name	**:**	Cellulose
Empirical formula	**:**	$(c_6H_{10}O_5)n$
Molecular weight	**:**	≈36000 where n≈220.
Functional category	**:**	Adsorbent; suspending agent; capsule and tablet diluents; tablet disintegrant**.**
Physical state	**:**	It is a purified, partially depolymerised. Cellulose that occurs white odourless, Tasteless, crystalline powder composed of porous particles. It is commercially available in different particle size and moisture grades which have different properties and applications.

Typical properties:

Density (bulk)	**:**	0.337 g/cm^3
Density (tapped)	**:**	0.478 g/cm^3
Density (true)	**:**	1.512-1.668 g/cm^3
Melting point	**:**	Chars at 260-270^{o}C
Moisture content	**:**	Less than 5% w/w
Solubility	**:**	Slightly soluble in 5%w/sodium Hydroxide solution, practically insoluble in water, dilute acids, and most Organic solvents.

Stability and storage

Condition	**:**	Microcrystalline cellulose is a stable, though hygroscopic material. The bulk material should be stored in a well closed container in a cool,dry,place.
Incompatibility	**:**	Incompatible with strong Oxidizing agents.

Pharmaceutical

Applications	**:**	It is widely used in pharmaceuticals, primarily as a binder/ diluents in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes. Microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. It is also used in cosmetics and food products.

TALC

Non-proprietary Names

BP	**:**	Purified Talc
JP	**:**	Talc
PhEur	**:**	Talc
USP	**:**	Talc

Synonyms:

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Imperial; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore; talcum.

Empirical Formula and Molecular Weight:

Talc is a purified, hydrated, magnesium silicate, approximating to the formula Mg6 (Si2O5)4(OH) 4. It may contain small, variable amounts of aluminium silicate and iron.

Functional Category:

Anti caking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Pharmaceutical Applications:

Talc was once widely used in oral solid dosage formulations as a lubricant and diluents. However, it is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbent. In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

Use	Concentration (%)
Dusting powder	90.0 – 99.0
Glidant and tablet lubricant	1.0 – 10.0
Tablet and capsule diluent	5.0 – 30.0

MAGNESIUM STEARATE

Non-proprietary Names

BP **:** Magnesium stearate

JP **:** Magnesium stearate

PhEur **:** Magnesium stearate

USP-NF **:** Magnesium stearate

Synonyms:

Dibasic magnesium stearate; magnesium distearate; magnesia stearas; magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt; Synpro 90.

Empirical Formula and Molecular Weight:

$C_{36}H_{70}MgO_4$ and 591.24

The USP32–NF27 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$). The PhEur 6.5 describes magnesium stearate as a mixture of solid organic acids consisting mainly of variable proportions of magnesium stearate and magnesium palmitate obtained from sources of vegetable or animal origin.

Structural Formula **:** $[CH_3(CH_2)_{16}COO]_2Mg$

Functional Category **:** Tablet and capsule lubricant.

Pharmaceutical Applications

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

8. METHODOLOGY

Materials and Methods

Table 2: Source of Gums

SL NO	POLYMER	ISOLATED FROM	BOTANICAL NAME	FAMILY
1	*Cassia roxburghii*	Seed	*Cassia roxburghii*	Caesalpiniaceae
2	Tamarind gum	Seed	*Tamarindus indica*	Leguminosae
3	Neem gum	Bark	*Azaridachta indica*	Meliaceae
4	Tapioca starch	Tubers	*Manihot esculenta*	Aspargaceae

ISOLATION OF POLYMERS FROM THEIR RESPECTIVE SOURCES:

Isolation of *Cassia roxburghii* Gum[9]

The seeds are collected and are dried at room temperature and are powdered using a grinder. A specific quantity of the seeds was weighed and is soaked in boiling water for 30 minutes, with occasional stirring. It is allowed to stand overnight and is filtered using an eight fold muslin cloth. Acetone is added to precipitate the mucilage present in it. The obtained mass is then centrifuged at 1500 rotations per second in a cooling centrifuge. The gum is separated and dried in hot air oven at 60 degree Celsius. Then it is passed through sieve number 100.

Collection of seeds → Size reduction → Powdering → Soaking in water for one day → Extraction by filtration → Centrifugation → Gum was dried → Passed through sieve number 100

Fig.8: *Cassia roxburghii* powder

Isolation of Tamarind Gum[38]

Tamarind gum is obtained from endosperm of the seeds of tamarind tree. The seeds are collected from the tree and are heated with sand for some period of time. This is done for removing the coat. Then it is hammer milled and is grinded with the help of the grinder. Then it is passed through sieve number 100.

Collection of seeds → Heating with sand → Coat removal → Hammer milling → Grinding → Sieved using sieve number 100

Fig.9: Tamarind powder

Isolation of Neem Gum[39]

An incision is made in the bark of the neem tree and after a month the exudate is collected. Then the whole mass is collected and is hydrated in distilled water. This is done to remove extraneous materials present in the gum. The mass is taken and

dried in hot air oven at 60°C. The completely dried mass is passed through sieve number 100.

Exudate is collected → Hydrated in distilled water → Extraneous materials were removed → Dried and powdered → Passed through sieve number 100

Fig.10: Neem powder

Isolation of Tapioca Starch[8]

The tapioca tubers are collected. It is peeled, washed and cut into small pieces. It is soaked in water for one hour. This is done to remove the extraneous particle from the surface. The mass is milled in a grinder and is dried in a hot air oven, then passed through sieve no 100.

Collection of tapioca tubers → Peeled, washed and cut into small pieces → Soaked in water for one hour → Milled and dried → Sieved using mesh number 100

Fig.11: Tapioca powder

Table 3: List of equipments used

Sl No	INSTRUMENTS	SUPPLIER/ MANUFACTURER
1	Single pan analytical balance	Schimadzu
2	Tablet punching machine	Rimek 12, Ahmedabad
3	Hardness tester	Campbell electronics –Mumbai
4	Roche friabilator	Campbell electronics –Mumbai
5	Dissolution apparatus	Campbell electronics –Mumbai
6	Tap density apparatus	Thermonik
7	Vernier caliper	Shreji
8	UV spectrophotometer	Schimadzu, Japan

Table 4: List of excipients used and their function

Table Deter Determination of λ max

Sl No	MATERIAL	SUPPLIER/ MANUFACTURER	CATEGORY
1	Paliperidone	Mylan laboratory,Hyderabad	API
2	HPMC	Loba chemie, Mumbai	Sustained- release polymer
3	MCC	Mitutiyo,india	Diluent
4	Mag. St.	Parag Fine Organics,Mumbai	Lubricant
5	Talc	CP Kelco US Inc. USA	Glidant

a. Stock solution of 1mg/ml of paliperidone was prepared by dissolving 100mg of drug in 100 ml of simulated gastric fluid (0.825M hydrochloric acid and 0.2% sodium chloride).

b. The stock solution was serially diluted to get solutions in the range of 2-10µg/ml and λ_{max} of the solution was found out by scanning the solution from 200-400 nm using UV-VIS spectrometer.

c. The λ_{max} of the solution was found to be 237 nm.

Determination of standard curve

a. Stock solution of 1000µg/ml of paliperidone was prepared by dissolving 100mg of drug in 100 ml of simulated gastric fluid.
b. From this take 10 ml and make up to 100 ml using simulated gastric fluid.
c. From the above solution take 10ml and dilute to 100 ml using simulated gastric fluid.
d. The stock solution was serially diluted to get solutions in the range of 2-10µg/ml.
e. The absorbance of the different diluted solutions was measured in a UV-VIS spectrophotometer at 237nm.
f. Calibration curve was plotted by taking concentration of the solution in µg on X-axis and absorbance on Y-axis and correlation co-efficient "r" was calculated.

COMPATIBILITY STUDIES[40]

IR spectra matching approach was used for detection of any possible chemical interaction between drug and polymer. A physical mixture of drug and polymer was prepared and mixed with the suitable quantity of potassium bromide. About 100mg of mixture was compressed to form a transparent pellet using a hydraulic press at 6 tons pressure .It was scanned from 4000 to 400 cm^{-1} in FTIR spectrometer. The IR spectrum of the physical mixture was compared with those of pure drug and polymers and matching was done to detect any appearance or disappearance of peaks. The IR spectrums of the sample and of the paliperidone working/reference standard in the range of 4000 cm^{-1} to 400 cm^{-1} were taken by preparing dispersion in dry potassium bromide under the same operational conditions mentioned above.

PREFORMULATION STUDIES[41,42]

Prior to development of a new dosage form with a drug moiety, it is essential that certain fundamental physical and chemical properties of the drug candidate and excipients are determined. The preformulation parameters like bulk density, tapped density, compressibility index hausner ratios etc. were determined as per IP procedure. The procedures for various tests are given below:

Angle of repose

This is carried out to determine the flow property of the granules. It is determined by the funnel method. A funnel was kept vertically at a specified height and the funnel bottom was closed. 10 gm of sample powder was filled inside the funnel. Then funnel was opened to release the powder to form a smooth conical heap which just touches the tip of the funnel. From the powder cone, the radius of the heap (r) and the height of the heap (h) were measured.

The angle of repose is represented as "θ" and is calculated using the following equation:

$$\mathbf{Tan\ \theta = h/r}$$

$$\mathbf{\theta = Tan^{-1}\ h/r}$$

Where

h = Height of the pile

r = Radius of the pile.

Table 5: Flow properties and corresponding Angle of repose

Flow property	Angle of repose (Degrees)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very, very poor	>66

BULK DENSITY

A specific quantity of the granules are weighed and transferred into a 50 ml graduated measuring cylinder. The initial volume and final volume are noted.

Bulk Density = Weight of Sample / Bulk Volume

TAPPED DENSITY

A specific quantity of granules is weighed and transferred into a 50 ml graduated measuring cylinder and is placed in the tapped density apparatus and was operated for a specific number of taps. The final volume was noted.

Tapped Density = Weight of Sample/ Tapped Volume

CARR'S INDEX

The Carr's index of the powder was determined by using formula:

Carr's index (%) = [(TBD - LBD) × 100]/TBD

LBD = Loose Bulk Density

TBD = Tapped Bulk Density

Table 6: Standard Values for Carr's Index:

CARR'S INDEX %	TYPE OF FLOW
5-15	Excellent
12-18	Good
18-23	Satisfactory
23-35	Poor
35-38	Very poor
>40	Extremely poor

COMPRESSIBILITY INDEX

The compressibility index is determined from the bulk volume and tap volume.

% C.I = (Tapped density - Bulk density) / Tapped density X 100

Table7: Scale of Flowability based on Compressibility Index

Compressibility index (%)	Flow character
≤10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very, very poor

HAUSNER'S RATIO:

Hausner's ratio is the ratio of the initial volume of the powder mass to the final volume of the powder mass obtained after the specified number of tapping.

Table 8: Scale of Flowability based on Hausner's Ratio

Hausner's ratio	Flow character
1-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor
>1.60	Very, very poor

COMPRESSION OF PALIPERIDONE SUSTAINED RELEASE TABLET

Weigh accurately about 200 mg of the mixture blend and fed into the die of single punch tablet press and compressed at 1.5N compression force using 8mm concave punches.

POST COMPRESSION PARAMETERS[42]

Weight Variation

Weight variation test for the tablets was performed as per the IP procedure. Ten tablets were weighed individually and the average weight was determined. The individual weight of all the ten tablets was noted. The percentage deviation of the individual weights from the average weight was then calculated. Deviation should not exceed the values given in Table: 9

Table 9: Percentage deviation allowed in weight variation:

AVERAGE WEIGHT OF TABLET	PERCENTAGE DEVIATION
80 mg or less	10
More than 80 mg but less than 250mg	7.5
250 mg or more	5

Tablet hardness:

Tablet hardness has been defined as the force required for breaking a tablet in a diametric compression test. A tablet was placed between two anvils of the hardness tester, force was applied to the anvils, and the crushing strength that caused the tablet to break was recorded.

Friability test:

The friability of the tablets were measured in a friability apparatus (Roche Friaberator Camp-bell Electronics, Mumbai). Ten tablets were initially weighed ($W_{initial}$) and placed into the friabilator. The friabilator was operated at 25 rpm for 4 minutes and then the tablets were dedusted and weighed (W_{final}). Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1%. Determination was made in triplicate.

$$\textbf{\% Friability} = \left[\frac{W_{initial} - W_{final}}{W_{initial}} \right] X\ 100$$

Assay of tablet

Ten tablets were randomly weighed and crushed. Calculated the average weight and taken the powder equivalent to 10 mg of paliperidone base in a 100 ml volumetric flask. Add few ml simulated gastric fluid and sonicated for 30 minute. Then volume made up to 100 ml with simulated gastric fluid. The 1mL of resultant solution diluted to 100mL with simulated gastric fluid and the absorbance was measured using UV spectrophotometer at 237nm.

***In-vitro* dissolution study[43]**

Parameters:

Instrument	:	USP XIX Dissolution rate test apparatus
Type	:	II Paddle
Medium	:	500 ml simulated gastric fluid (0.825M hydrochloric acid and 0.2% sodium chloride)
Temperature	:	37±0.5°C.
RPM	:	50
Testing time	:	24 h
Time points	:	1, 2, 3, 4, 5, 6, 7, 8,9,24
Amount withdrawn	:	5 ml.
λ max	:	237 nm.

Release kinetic analysis[44]

To study the release kinetics, data obtained from *in-vitro* drug release studies were plotted in various kinetic models: zero order (Equation 8) as cumulative amount of drug released vs. time, first order (Equation 9) as log cumulative percentage of drug remaining vs. time, and Higuchi's model (Equation 10) as cumulative percentage of drug released vs. square root of time.

$$C = K_0 t$$

Where

K_0	:	is the zero-order rate constant expressed in units of concentration/time
T	:	is the time in hours.

A graph of concentration vs. time would yield a straight line with a slope equal to K_0 and intercept the origin of the axis.

$$\mathbf{LogC = LogCo - kt/2:303}$$

Where

C_0 : is the initial concentration of drug,

K : is the first order constant, and t is the time.

$$\mathbf{Q = Kt^{1/2}}$$

Where

K : is the constant reflecting the design variables of the system

t : is the time in hours.

Mechanism of Drug Release

To evaluate the mechanism of drug release from Paliperidone sustained release tablets, data of drug release were plotted in Zero Order Kinetic equation as log cumulative percentage of drug released vs. time, and the exponent n was calculated through the slope of the straight line.

$$\mathbf{Mt\text{-}M\infty = Kt^n}$$

Where

Mt/M∞ - is the fractional solute release,

t - is the release time,

K - is a kinetic constant characteristic of the drug/ polymer system, and n is an exponent that characterizes the mechanism of release of tracers.

Stability Studies[45]

The prepared formulations which showed best results *in vitro* was selected and kept for stability testing for a period of three months. The tablets were kept at 40± 2°C/75%±5%RH in a stability chamber in packed condition. These samples were analyzed for color, hardness, assay, % moisture absorbed and *in vitro* drug release, at the end of first, second and third month. Further these results were compared with the initial results to evaluate the stability of product.

9. FORMULATION AND DEVELOPMENT

Sustained release tablets of paliperidone were prepared by direct compression using different natural polymers like *Cassia roxburghii, Tamarindus indica, Azadirachta indica, Manihot esculenta* and comparing with a standard rate retardant polymer HPMC at three different concentrations of polymers (30%, 50% and 75%).

Table 10: Preparation of sustained release tablets using different natural polymers

Drug	Polymers	Polymer percentage (%)
PALIPERIDONE	HPMC	35,50,75
	Cassia roxburghii	35,50,75
	Tamarindus indica	35,50,75
	Azadirachta indica	35,50,75
	Manihot esculenta	35,50,75

The ingredients in the table above were accurately weighed and passed through sieve #60, then magnesium stearate and talc was passed through sieve #80. Then the materials were blended except magnesium stearate and talc for 20 minutes in ascending order. Later the powder mixture was blended with magnesium stearate and talc for 5 minutes.

Table 11: Formula for development of tablet

FORMULA	DRUG	HPMC	CR	TI	AI	ME	MCC	TALC	Mg.St.
F1	6	35%					120	2	2
F2	6	50%					90	2	2
F3	6	75%					40	2	2
F4	6		35%				120	2	2
F5	6		50%				90	2	2
F6	6		75%				40	2	2
F7	6			35%			120	2	2
F8	6			50%			90	2	2
F9	6			75%			40	2	2
F10	6				35%		120	2	2
F11	6				50%		90	2	2
F12	6				75%		40	2	2
F13	6					35%	120	2	2
F14	6					50%	90	2	2
F15	6					75%	40	2	2

Various polymers have been evaluated based on post compression parameters and *in vitro* dissolution data of prepared tablets. The suitable polymer and its concentration has optimised from its

- Process efficiency
- Friability
- Assay of drug loaded

10. RESULTS AND DISCUSSION

Determination of λ max:

The wavelength showing maximum absorbance (λ max) for paliperidone was determined by scanning the standard stock solution of the drug using UV visible spectrophotometer. The λ max was found to be 237nm for paliperidone which is in accordance with the data available in literature.

Table 12: Calibration curve data for paliperidone

Concentration (µg/ml)	Absorbance
0	0
2	0.069
4	0.114
6	0.173
8	0.228
10	0.277

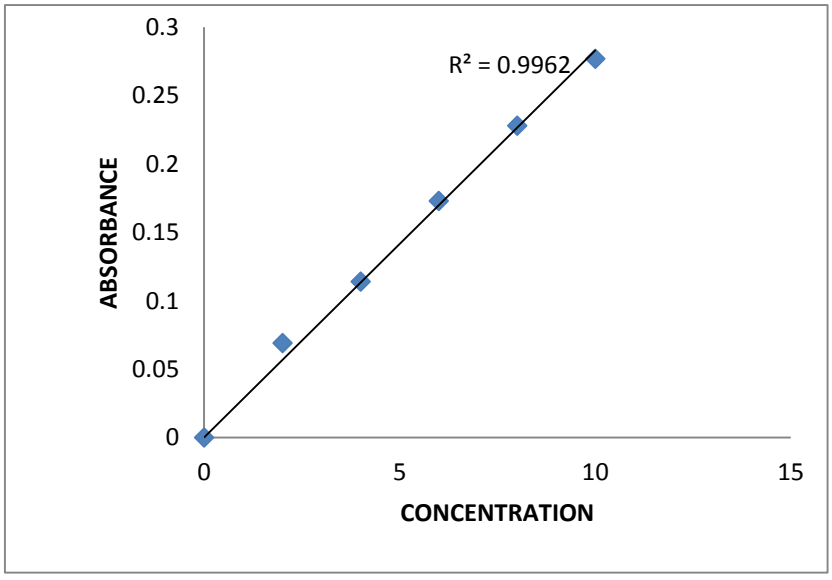


Fig.12: Caliberation Curve of Paliperidone

Compatibility studies:

IR spectra matching approach was used for detection of any possible chemical interaction between the drug and the polymer. The samples were prepared by pressed pellet technique. The IR spectra was determined using JASCO FT/IR-4100. The scanning range was between 500- 4000cm^{-1}. The spectrum obtained was shown in figure.

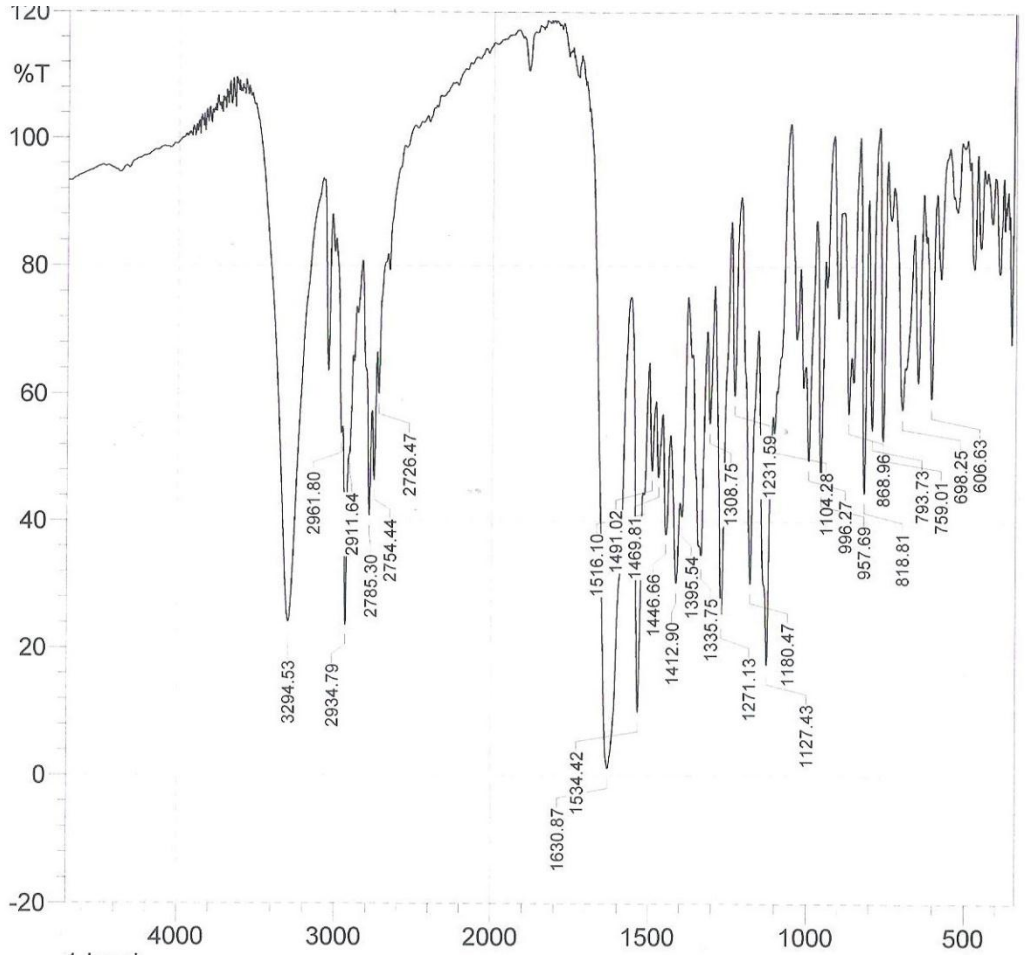


Fig. 13:IR Spectra of Paliperidone

Table 13: Characteristic peaks of Paliperidone

S.No	Peaks	Characteristic functional group
1	3294	NH Stretching
2	1630	C=O
3	1534	C=N
4	2911,2853	CH2 Stretching
5	2961	CH3 assymetric stretching

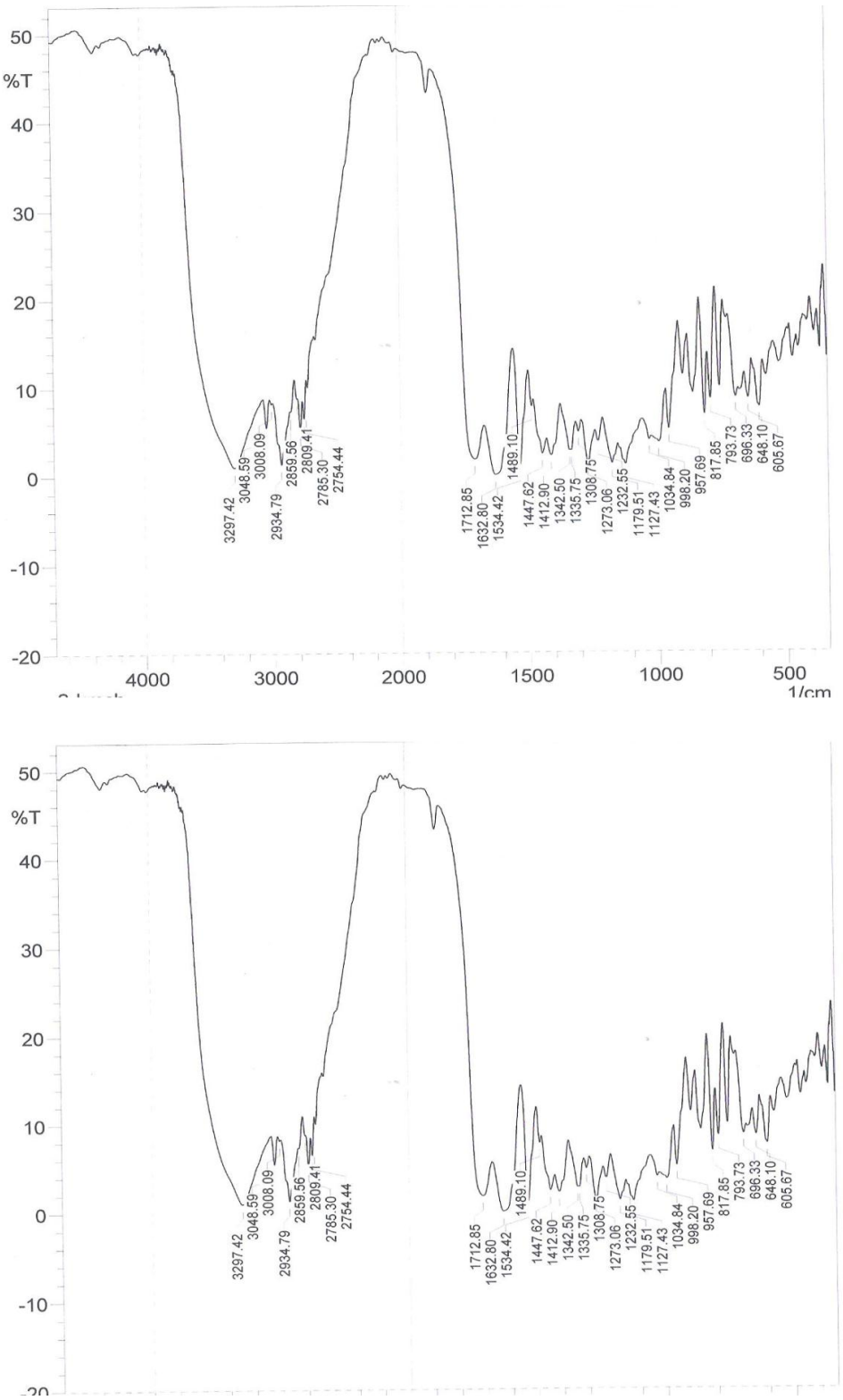


Fig.14:IR spectra of Paliperidone + Azadirachta Indica before stability study and after stability study

Discussion:

The data given in the table shows the characteristic peaks detected in the IR spectrum of pure drug, Paliperidone. The spectra of the pure drug and the spectra of the drug mixed with polymer are compared for the presence or absence of characteristic peak. It was found that the spectra of the drug with polymer showed all the characteristic peak of Palipeidone suggesting that there is no compatibility problem between the drug and polymer.

Preformulation studies

The preformulation parameters like angle of repose, bulk density, tapped density and compressibility index and Hausner's ratios were studied to evaluate the flowability and compressibility of the powder formulations. The bulk density and tapped density was found to be in the range of 0.421 to 0.683 gm/cm^3 and 0.529 to 0.899 gm/cm^3

The compressibility and hausner's ratio were found to be 17.81% to 30.47% and 1.17 to 1.43. This indicates the granules have good flow character and have good compression property. All the results are within the prescribed limits.

Preformulation Parameters

Table 14: Results of Preformulation Studies

FORMULATION CODE	ANGLE OF REPOSE	BULK DEDNSITY	TAPPED DENSITY	C I	HAUSNERS RATIOS
F1	28°16'	0.625	0.899	30.47	1.43
F2	30° 23'	0.681	0.883	22.87	1.29
F3	32° 11'	0.423	0.521	18.80	1.23
F4	33° 13'	0.431	0.552	21.92	1.28
F5	33° 61'	0.617	0.819	24.66	1.32
F6	34° 07'	0.625	0.830	24.69	1.33
F7	38° 12'	0.602	0.809	25.58	1.34
F8	38° 73'	0.421	0.529	20.41	1.25
F9	39° 05'	0.683	0.889	23.17	1.30
F10	26° 18'	0.512	0.623	17.81	1.21
F11	27° 07'	0.458	0.537	14.71	1.17
F12	39° 16'	0.465	0.571	18.56	1.22
F13	33° 33'	0.620	0.891	30.41	1.43
F14	34° 17'	0.615	0.811	24.16	1.31
F15	34° 23'	0.601	0.807	25.52	1.34

Evaluation of Post Compression Parameters

The tablets were evaluated for thickness, hardness, friability, average weight and assay. The thickness of the formulated tablets was found to be in the range of 0.31mm to 0.41mm. Hardness and friability was found to be 3.5-6kg/cm^2 and 0.046-0.523% which indicates the tablet has adequate mechanical strength. Weight variation of the tablets was found to be within the specified limits. . The drug content of all the formulations ranged from 89.78-96.81% indicating the presence of an acceptable amount of drug in the formulations.

Post Compression Parameters

Table 15: Results of Evaluation of Tablets

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Average wt(mg)	Assay (%)
F1	0.31	4.0	0.523	199	95.12
F2	0.35	5.5	0.420	209	94.87
F3	0.41	6.0	0.413	203	95.02
F4	0.36	3.5	0.141	194	93.12
F5	0.39	5.0	0.159	198	92.09
F6	0.37	5.5	0.261	212	92.68
F7	0.40	4.5	0.102	200	90.12
F8	0.35	5.0	0.124	207	89.78
F9	0.39	6.0	0.198	203	90.03
F10	0.38	4.5	0.046	209	95.71
F11	0.35	5.5	0.047	201	96.29
F12	0.34	6.0	0.062	207	96.81
F13	0.41	3.5	0.212	208	94.71
F14	0.40	4.5	0.314	207	94.13
F15	0.36	5.0	0.282	209	95.11

***In vitro* Dissolution Study of Tablets**

Paliperidone controlled release tablets were formulated using 5 different polymers such as HPMC, *Cassia roxburghii*, Tamarind seed powder, Neem gum, Tapioca starch in the percentage of 35%, 50%, and 75%. A total of 15 formulations were made using these polymers by direct compression method and 24 hours dissolution studies were carried out.

Effect of HPMC on Drug Release

Cumulative percentage drug release for the different concentration of HPMC (35%, 50%,75%) is given the table below. Formulation F1, F2, F3 containing the different concentrations of HPMC are taken. The F1 and F2 do not show the drug release up to the desired period of time. . In case of formulation F3 containing HPMC(75%) also showed prolonged release but could not prolong the release for desired time.

Table 16: *In vitro* Release Data of F1, F2 and F3

TIME	F1	F2	F3
0	0	0	0
1	6.6	4.12	4.30
2	31.12	30.75	8.71
3	52.01	35.20	17.51
4	58.07	40.12	26.51
5	70.98	57.10	31.10
6	81.12	68.01	35.81
7	85.88	70.33	49.40
8	87.27	77.60	52.09
9	91.95	86.32	60.15
24	95.60	95.96	96.50

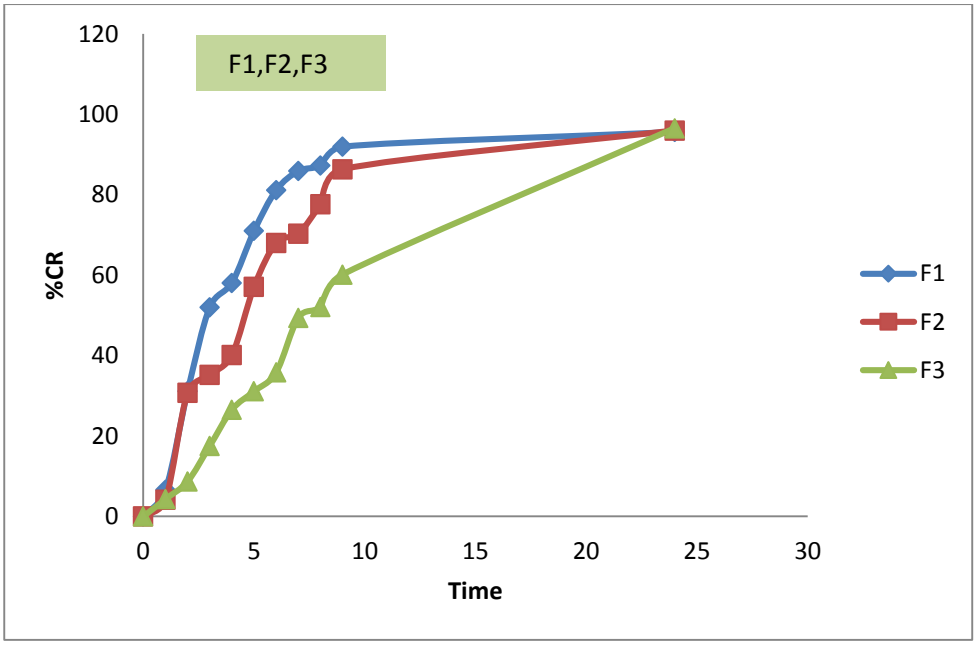


Fig.15: Dissolution graph of HPMC (F1,F2,F3)

Effect of *Cassia roxburghii* on Drug Release

Cumulative percentage drug release for the different concentration of *Cassia roxburghii* (35%, 50% and 75%) is given the table below. These formulations were able to extend and control their release pattern to desired period of time. The drug release rate was found to be decreased when concentration of polymers was increased. This may be due to increased swelling of the polymer when concentration is increased which leads to increased viscosity of the medium and thus increases the mean diffusional path length of the drug molecule to get released into the diffusion medium.

Table 17: *In vitro* Release Data of F4, F5 andF6

TIME	F4	F5	F6
0	0	0	0
1	8.76	7.16	7.06
2	13.22	11.04	11.08
3	19.94	15.55	16.34
4	26.72	22.42	20.38
5	35.76	24.71	23.76
6	41.71	35.87	34.84
7	56.32	42.80	50.10
8	59.63	58.60	58.18
9	65.60	63.59	62.50
24	95.14	95.31	94.30

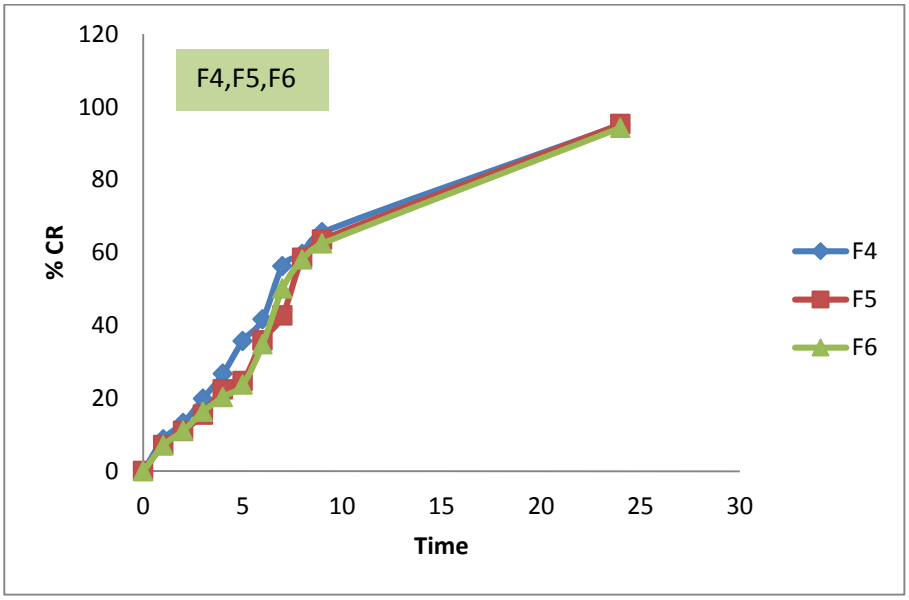


Fig.16: Dissolution graph of Cassia roxburghii (F4,F5,F6)

Effect of *Tamarindus indica* on drug release

Cumulative percentage drug release for the different concentration of Tamarindus indica(35%,50%,75%) is given the table below. The decrease in drug release rate as the concentration of the polymer increases may be attributed to the presence of a highly water soluble compound. It is seen that there is a faster rate of polymer swelling and a large increase in gel thickness to prevent immediate tablet disintegration, and thus controlling the diffusion of the drug.

Table 18: *In vitro* release data of F7, F8, F9

TIME	F7	F8	F9
0	0	0	0
1	4.30	4.58	5.62
2	29.76	6.65	7.63
3	34.35	17.31	14.27
4	41.20	27.83	19.98
5	57.13	34.51	21.38
6	66.47	39.20	25.98
7	70.34	52.94	30.41
8	77.10	59.84	31.95
9	83.17	70.41	49.13
24	94.12	95.20	96.27

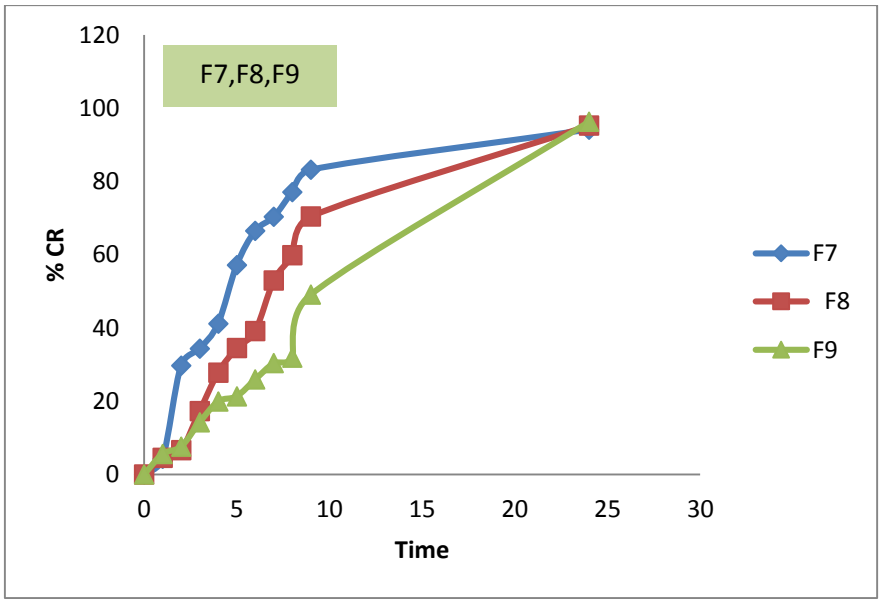


Fig.17: Dissolution graph of *Tamarindus indica* (F7,F8, F9)

Effect of *Azadirachta indica* on drug release

Cumulative percentage drug release for the different concentration of *Azadirachta indica* (35%,50%,75%) is given the table below. For formulation F12 containing 75% polymer the cumulative release was found to be 36.02% in 9 hr and 97.80% at 24 hours. The increase in polymer content delays the drug release as the polymer is hydrophilic and swellable polymer which produces increased swelling with increase polymer which might have increased diffusional path length for the drug to get diffuse across the membrane.

Table 19: *In vitro* release data of F10, F11, F12

TIME	F10	F11	F12
0	0	0	0
1	2.01	2.20	2.15
2	4.40	4.41	4.41
3	4.39	13.23	4.45
4	6.62	15.55	8.89
5	13.21	17.90	11.16
6	24.11	22.45	13.46
7	26.90	27.49	22.38
8	29.28	29.52	26.98
9	33.10	34.24	36.02
24	96.97	98.14	97.80

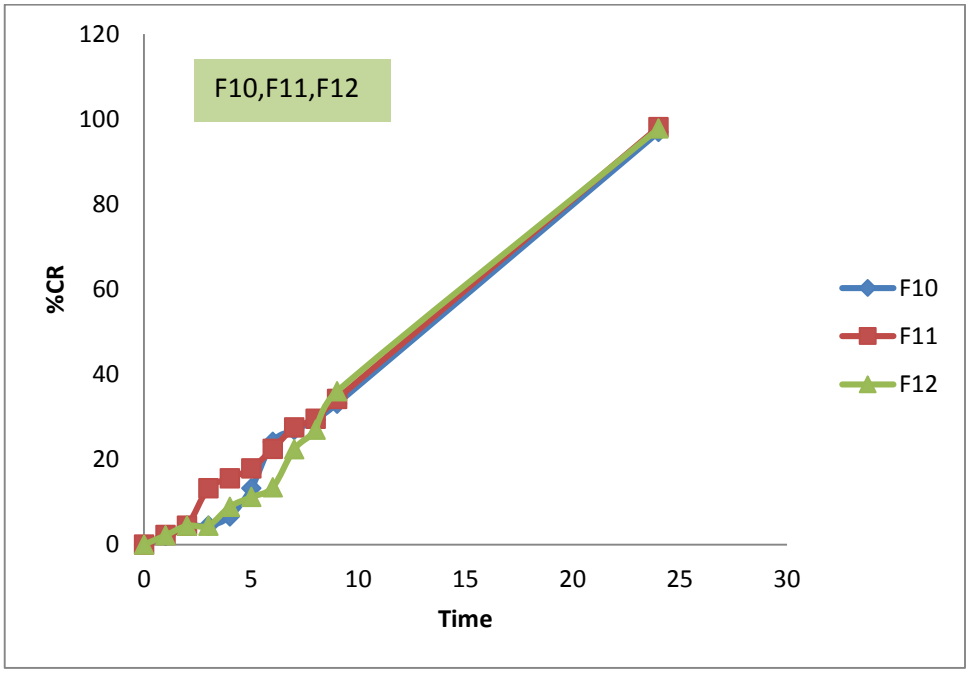


Fig.18: Dissolution graph of *Azadirachta indica* (F10,F11,F12)

Effect of *Manihot esculenta* on drug release

Cumulative percentage drug release for the different concentration of Manihot Esculenta (35%,50%,75%) is given the table below. *In vitro* dissolution data showed that these are not the best candidate for once daily dosage form as the release of the drug is not up to the desired extent. After 24 hours, the release of the drug was found to be 94-95% only. As a result, these formulations cannot be considered as optimized formulation.

Table 20: *In vitro* release data of F13,F14,F15

TIME	F13	F14	F15
0	0	0	0
1	2.19	2.10	2.09
2	4.40	6.60	5.30
3	8.83	6.84	5.31
4	13.41	11.30	10.18
5	20.08	20.03	19.70
6	26.87	24.98	24.44
7	42.43	39.31	26.87
8	56.81	50.89	41.30
9	71.98	66.30	48.23
24	95.13	95.79	94.18

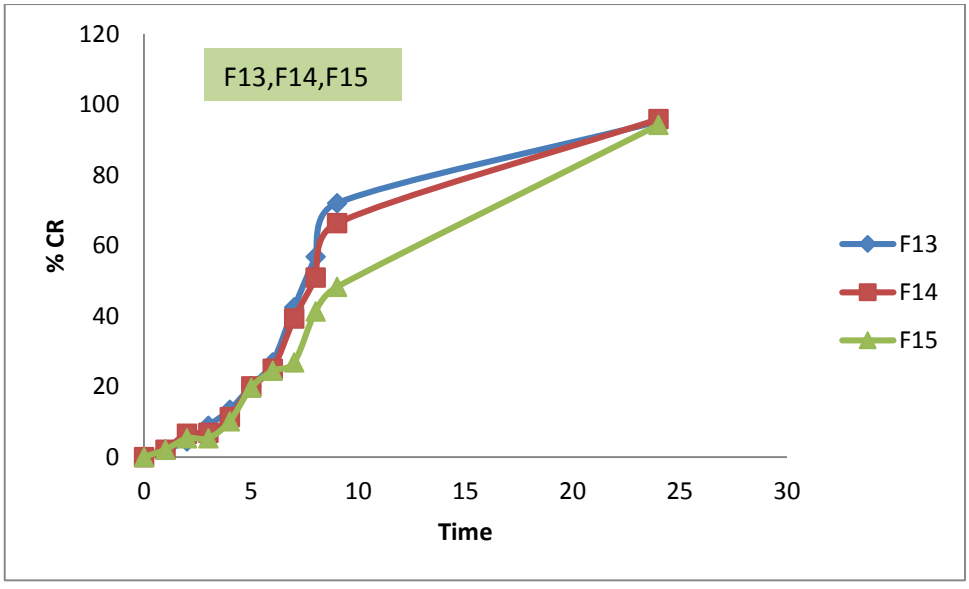


Fig.19: Dissolution graph of *Manihot esculenta* (F13,F14,F15)

From the *in vitro* dissolution data of the 15 formulations, almost all the formulations have the release up to the extended period of time. From these formulations F12 was chosen as the optimised formulation because of their extent their release up to 24 hours. All other post compression parameters like bulk density, tapped density, angle of repose, compressibility index and hausner's ratio are up to the specified limits.

Dissolution profile of optimized formulation

From the dissolution data and from the post compression parameters it is concluded that *Azadirachta indica* 75% was fond to be the optimised formulation.

Table 21: *In vitro* release data of optimised formulation

TIME	FORMULATION F12
0	0
1	2.15
2	4.41
3	4.45
4	8.89
5	11.16
6	13.46
7	22.38
8	26.98
9	36.02
24	97.8

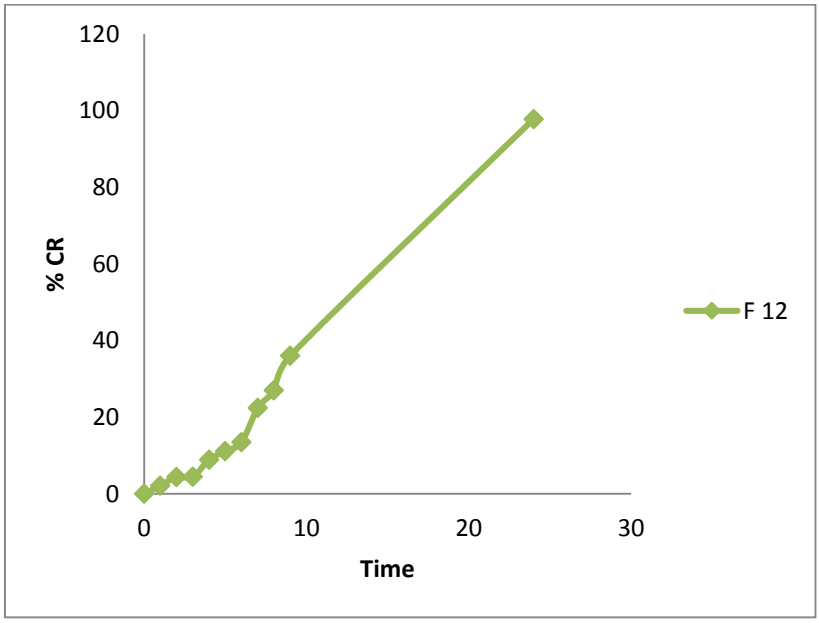


Fig.20: Dissolution graph of optimised formulation(F12)

Drug Release Kinetics analysis:

The *in-vitro* drug release data of the optimized formulation was subjected to kinetic analysis by plotting various kinetic equations like zero order, first order and Higuchi plot. The kinetic analysis data of the formulation was shown in the table. The kinetic model that best fits with the release data of formulation was evaluated by the correlation coefficient (R^2) values. According to the values obtained higher linearity was observed with linear plot(zero order) with R^2 value of 0.955. Thus the formulation may follow zero order drug release.

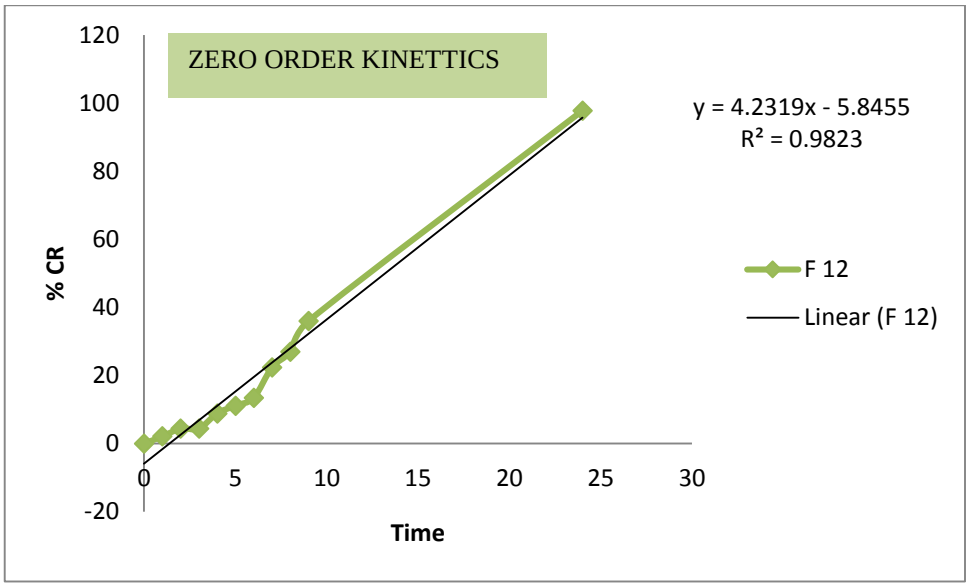


Fig.21:Zero order plot

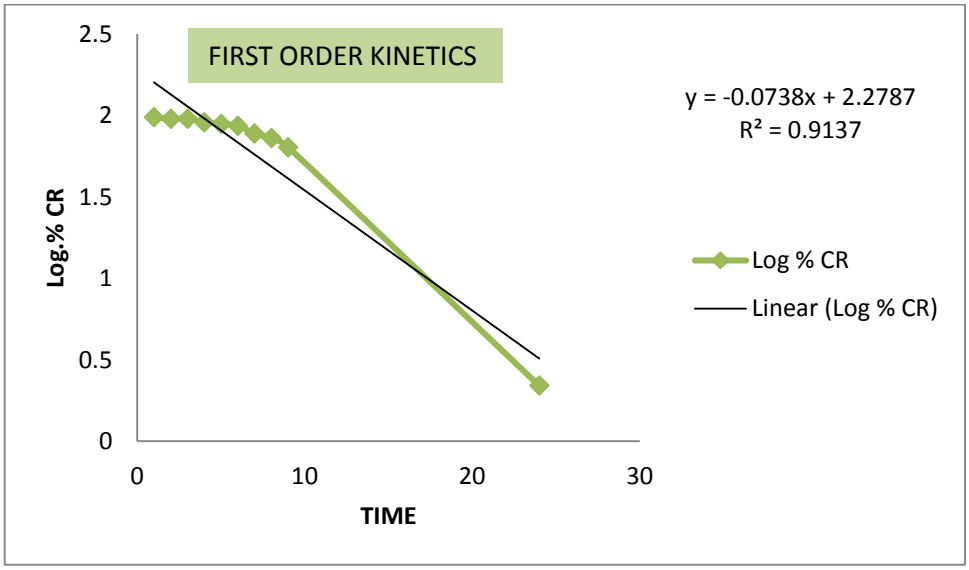


Fig 22:First order plot

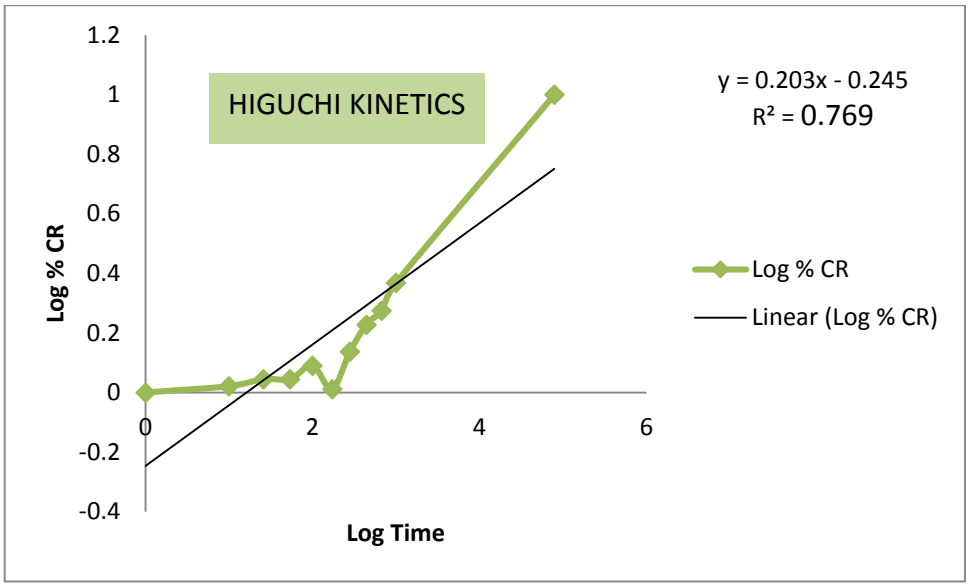


Fig 23: Higuichi plot

Table 22: Result of kinetic analysis

FORMULATION	Zero order (R^2)	First order (R^2)	Higuchi kinetics (R^2)
F 12	0.955	0.913	0.769

Mechanism of drug release

Mechanism of drug release data can be assissed by plotting the drug release data in linear, exponential and power equations. From the regression coefficiant value, it may follow zero order kinetics.

Stability study

Here the tablets were loaded at accelerated condition at $40^0C \pm 2^0C$/75% RH±5% in a stability chamber. Samples were withdrawn at 30^{th} and 60^{th}day and evaluated for the physical appearance, drug content and dissolution characteristics. The stability analysis data were given in table above. The result showed that storage at 40 ºC had no effect on the hardness, disintegration time and dissolution time.

Table23: Stability study of formulation F12(Paliperidone+Neem gum 75%)

SL. NO.	PARAMETERS	INITIAL	30th DAY	60th DAY	90th DAY
1	Physical appearance	Grey	Grey	Grey	Grey
2	Drug contenet(%)	96.81%	96.75%	96.34%	96.05%
3	Dissolution (%CR in 24thhr)	97.80%	97.38%	97.06%	96.92%

SEM IMAGE OF *Azadirachta Indica*

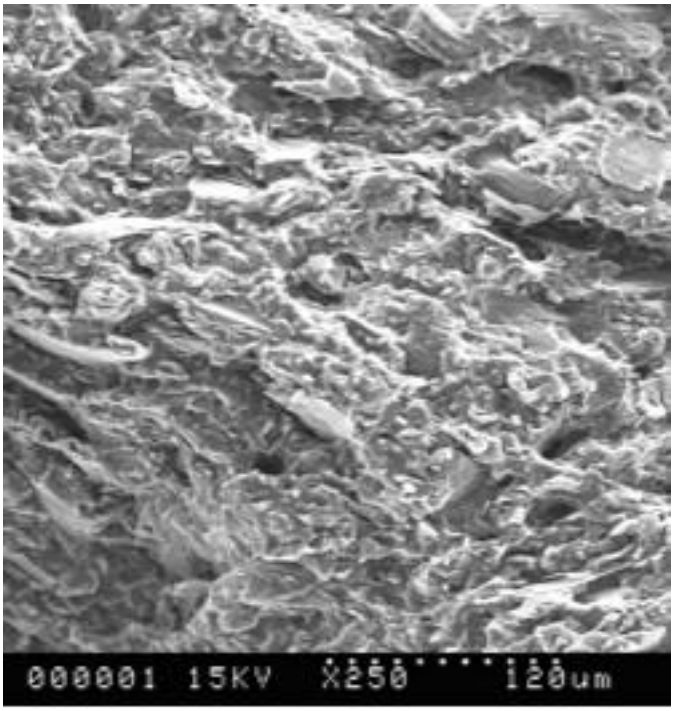


Fig24: SEM image of *Azadirachta indica*

11. SUMMARY

The Paliperidone has various side effects which may be related to high blood plasma concentration levels excluding its use as a single immediate release dose. Presently Paliperidone is available as INVEGA that utilizes OROS technology which has several disadvantages. Hence present study was aimed to formulate sustained release tablet of paliperidone by direct compression method.

Compatibility studies:

IR spectra matching approach was used for detection of any possible chemical interaction between the drug and the polymer. The samples were prepared by pressed pellet technique. The IR spectra were determined using JASCO FT/IR-4100. Scanning range was between 500- 4000cm^{-1}. FT-IR study revealed the absence of any chemical interaction between drug and polymer used.

Pre-compression analysis:

Preformulation studies of the sustained release and immediate release layer powder blend were done. The results of the evaluation suggests that all the granules exhibit good flow properties, so all the formulations were directly compressed to tablets.

Post formulation studies of Tablets

Tablets were evaluated for their physical parameters like hardness, thickness, friability, weight variation, and drug content uniformity complies with IP standards.

***In-vitro* dissolution studies:**

The *in-vitro* drug release studies were performed using USP type 2 paddle type dissolution apparatus using simulated gastric fluid (0.825M hydrochloric acid and 0.2% sodium chloride) for 24 hours. The formulation F12 (*Azadirachta indica* 75%) showed the maximum release of drug (97.8 %) at 24^{th} hour. From the release data it is clear that the best sustaining ability was revealed by the formulation F12.

Drug Release Kinetics Analysis:

The *in-vitro* drug release data of the optimized formulation was subjected to kinetic analysis by plotting various kinetic equations like zero order, first order and Higuchi plot. According to the values obtained higher linearity was observed with Higuchi plot, indicates drug is released by diffusion. The kinetic model that best fits with the release data of formulation was evaluated by the correlation coefficient (R^2) values. According to the values obtained higher linearity was observed with linear plot (zero order) with R^2 value of 0.955. Thus the formulation may follow zero order drug release.

Stability studies:

The tablets were loaded at accelerated condition at $40^0C \pm 2^0C$/75% RH±5% in a stability chamber. Samples were withdrawn at 30^{th} , 60^{th} and 90^{th} day and evaluated for the physical appearance, drug content and dissolution characteristics. The result obtained from the study reveals that storage at 40 ºC had no effect on the hardness, disintegration time and dissolution time. The stability studies indicate that the sustained release tablet was suitable for drug delivery of paliperidone without having any physical stability issues.

12. CONCLUSION

The formulation F12, 75% of ***Azadirachta indica*** could give rise to tablets exhibiting sustained drug release. Recent developments in the area of natural gums as excipients in the sustained release of drugs are to be explored and our research work provided the ground work for further studies in zero order release mechanisms.

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FORMULATION AND EVALUATION OF PALIPERIDONE SUSTAINED RELEASE TABLETS USING NATURAL GUMS AS BINDER

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CONTENTS

INTRODUCTION

- Sustained release tablets and capsules are commonly taken only once daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect.

- Binders are agents that are added either in dry form or in wet form during wet granulation to form granules or to provide cohesive impacts for directly compressed tablets.

- Natural binders provides the tablet formulations with good hardness and friability. These binders prolongs the dissolution rate of some slightly soluble drugs and can be chosen as good candidate for sustained release.

- Paliperidone is a prescription drug used for the treatment of schizophrenia.

- The natural polymers were collected from the following sources:
    a. *Cassia roxburghii* seed
    b. *Tamarindus indica* seed
    c. *Azadirachta indica* bark
    d. *Manihot esculenta* root tubers

AIM AND OBJECTIVE

- The aim of this investigation is to formulate and evaluate paliperidone sustained release tablets using natural polymers and to compare with standard rate retardant polymer HPMC.

Objective:

- To estimate the binding capacity of various natural gums in granules and tablet formulations as a release retardant.

- To collect and isolate gums from different natural sources.

- To prepare granules by direct compression method and determine their physical properties.
- To optimise the binder concentration using appropriate experimental design.
- To prepare and compress paliperidone tablets and compare with standard rate retardant polymer, HPMC.
- To evaluate the *invitro* release principle of sustained release paliperidone tablets.
- To perform the stability study on optimised paliperidone formulation.

LITERATURE REVIEW

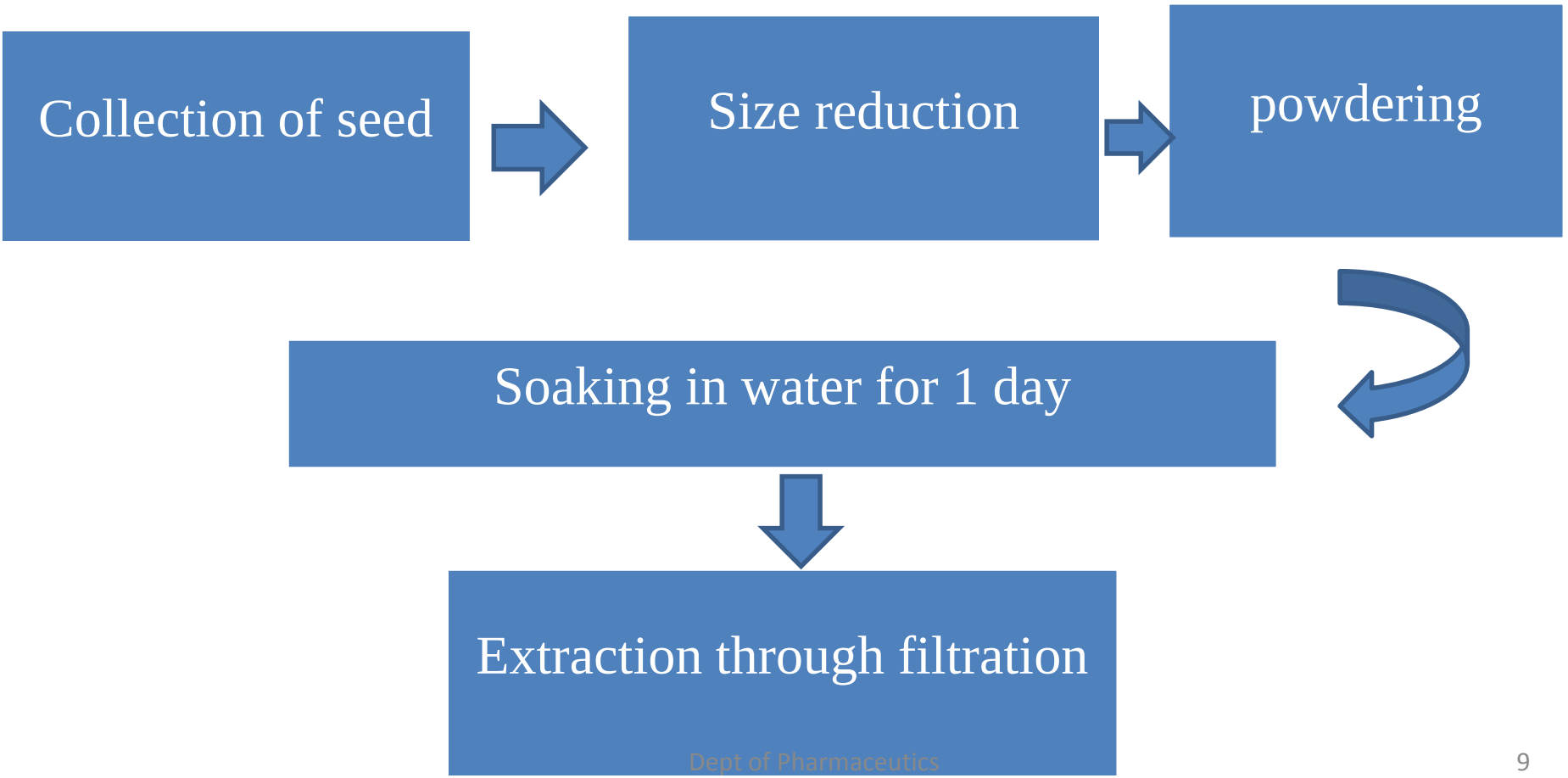
Sl No	Author's Name	Journal Name	Objective	Conclusion
1	Mughal et al	AAPS PharmSci Tech. 2011	Developed propranolol hydrochloride-loaded matrix tablets using guargum and xantham gum	Polymers can be used to formulate successful sustained release propranolol hydrochloride matrix tablets that have desirable characteristics.
2	Prajapati SK et al	Formulation and evaluation of once daily sustained release tablets of aceclofenac using natural gums	Formulated once daily sustained release tablets of aceclofenac with natural polymers like xanthum gum and karaya gum in different ratios.	These polymers can be used in formulating succesful sustained release formulations. Xanthum gum has high sustained effect on the release of aceclofenac than karaya gum.

Sl No	Author's Name	Journal Name	Objective	Conclusion
3	Hiremath *et al*	Int J Pharm. 2008	Developed sustained release tablet formulations of rifampicin and isoniazid combination using HPMC and HPC	They found out that controlled release formulations containing 50% HPMC and 60% HPC, found to be of good quality and provided required release profile for both rifampicin and isoniazid.
4	Patel Shailendra et al	Natural Binding Agents in Tablet Formulation	Isolated Cassia roxburghii, tamarind and tapioca from their respective sources and formulated diclofenac tablets using these polymers.	Natural substances like starches, mucilages, gums and also dried fruits can be used as binding agent. They have been shown good potential as binding agent as well as they posses some other properties like disintegrating agent, fillers, sustain releasing agent.

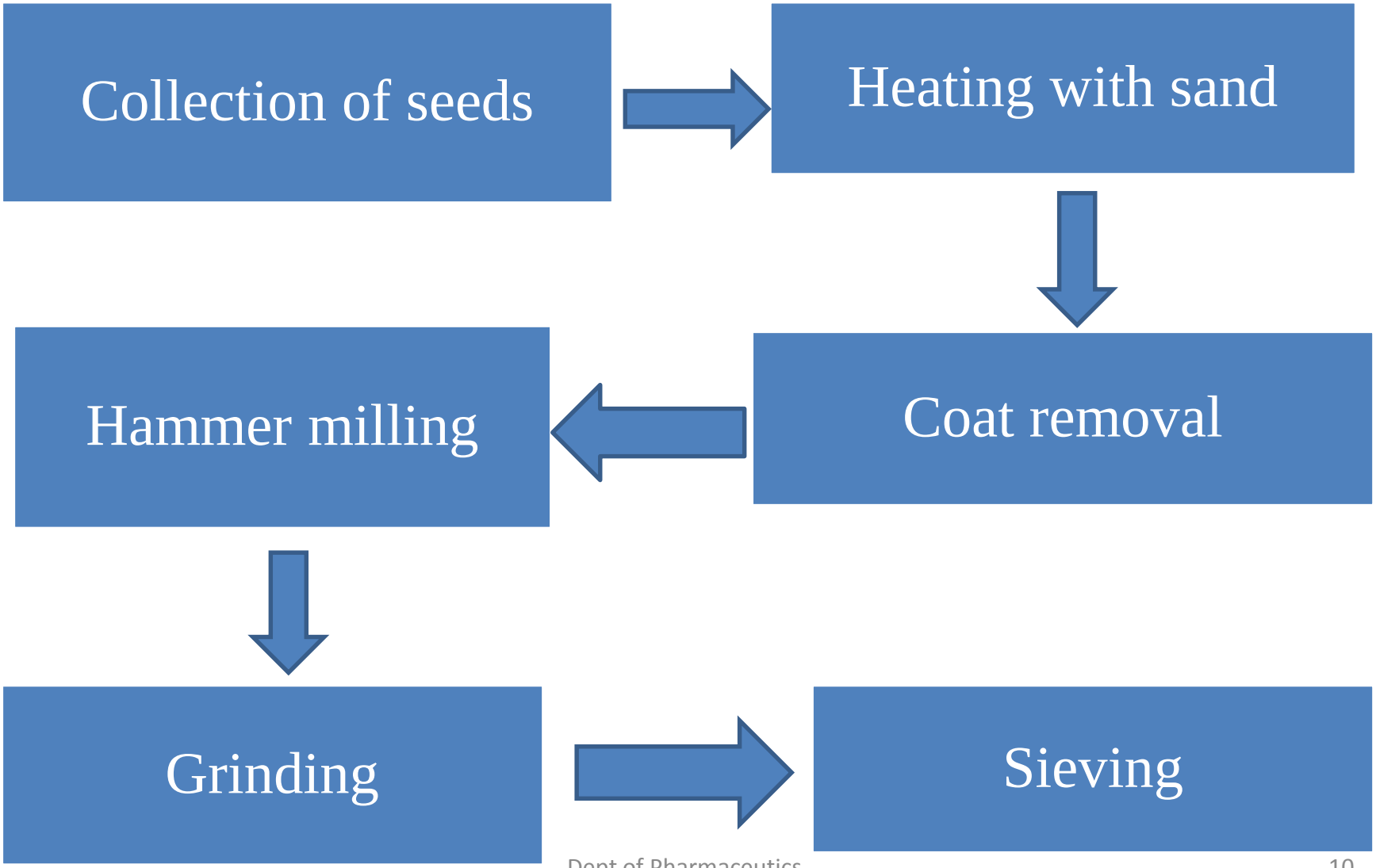
METHODOLOGY

ISOLATION OF NATURAL POLYMERS

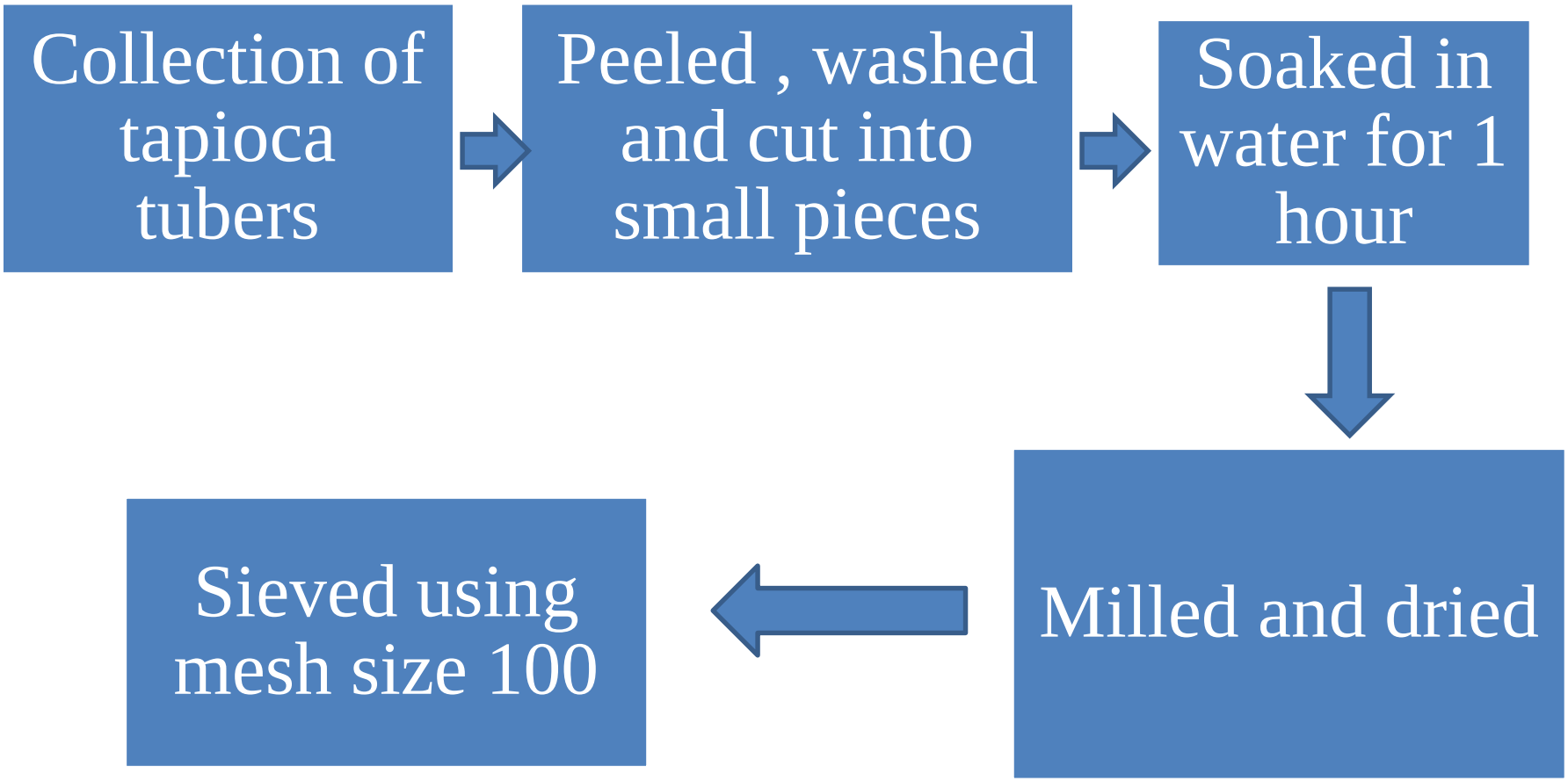
1. ISOLATION FROM *Cassia roxburghii*



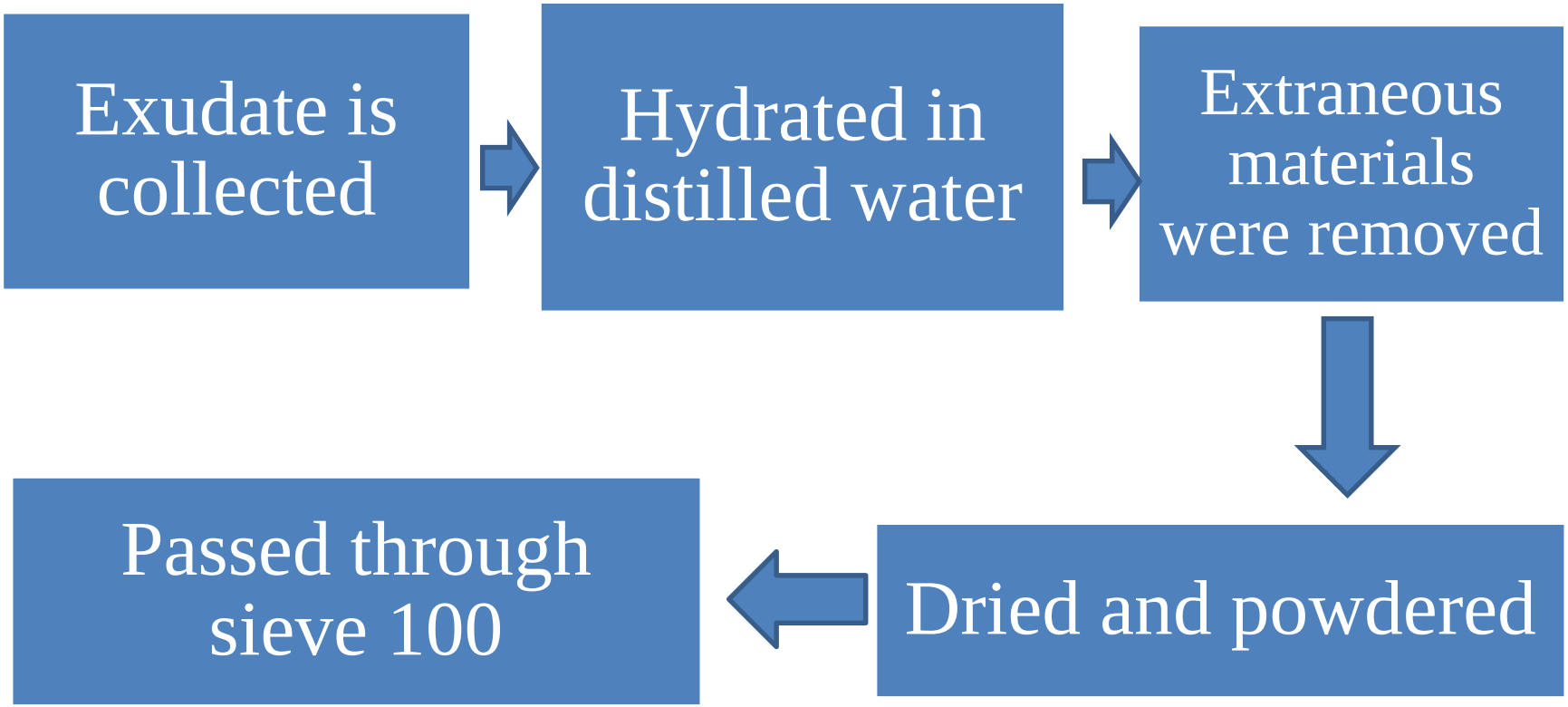
2. ISOLATION FROM *Tamarindus indica*



3.ISOLATION FROM *Manihot esculenta*



4.ISOLATION FROM *Azadirachta indica*



FORMULATION AND DEVELOPMENT

Preparation of sustained release tablets using different natural polymer

Drug	Polymers	Polymer percentage(%)
PALIPERIDONE	HPMC	35,50,75
	Cassia roxburghii	35,50,75
	Tamarindus indica	35,50,75
	Azadirachta indica	35,50,75
	Manihot esculenta	35,50,75

FORMULATION

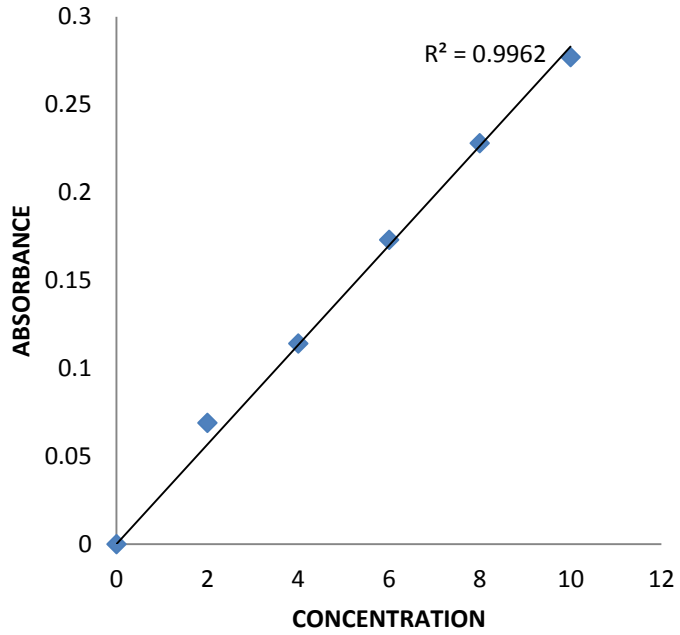
FORMULA	DRUG (mg)	HPMC (mg)	CR (mg)	TI (mg)	AI (mg)	ME (mg)	MCC (mg)	TALC (mg)	Mg.St. (mg)
F1	6	70					120	2	2
F2	6	100					90	2	2
F3	6	150					40	2	2
F4	6		70				120	2	2
F5	6		100				90	2	2
F6	6		150				40	2	2
F7	6			70			120	2	2
F8	6			100			90	2	2
F9	6			150			40	2	2
F10	6				70		120	2	2
F11	6				100		90	2	2
F12	6				150		40	2	2
F13	6					70	120	2	2
F14	6					100	90	2	2
F15	6					150	40	2	2

RESULTS AND DISCUSSION

Determination of calibration curve:

Calibration curve of paliperidone at 237nm

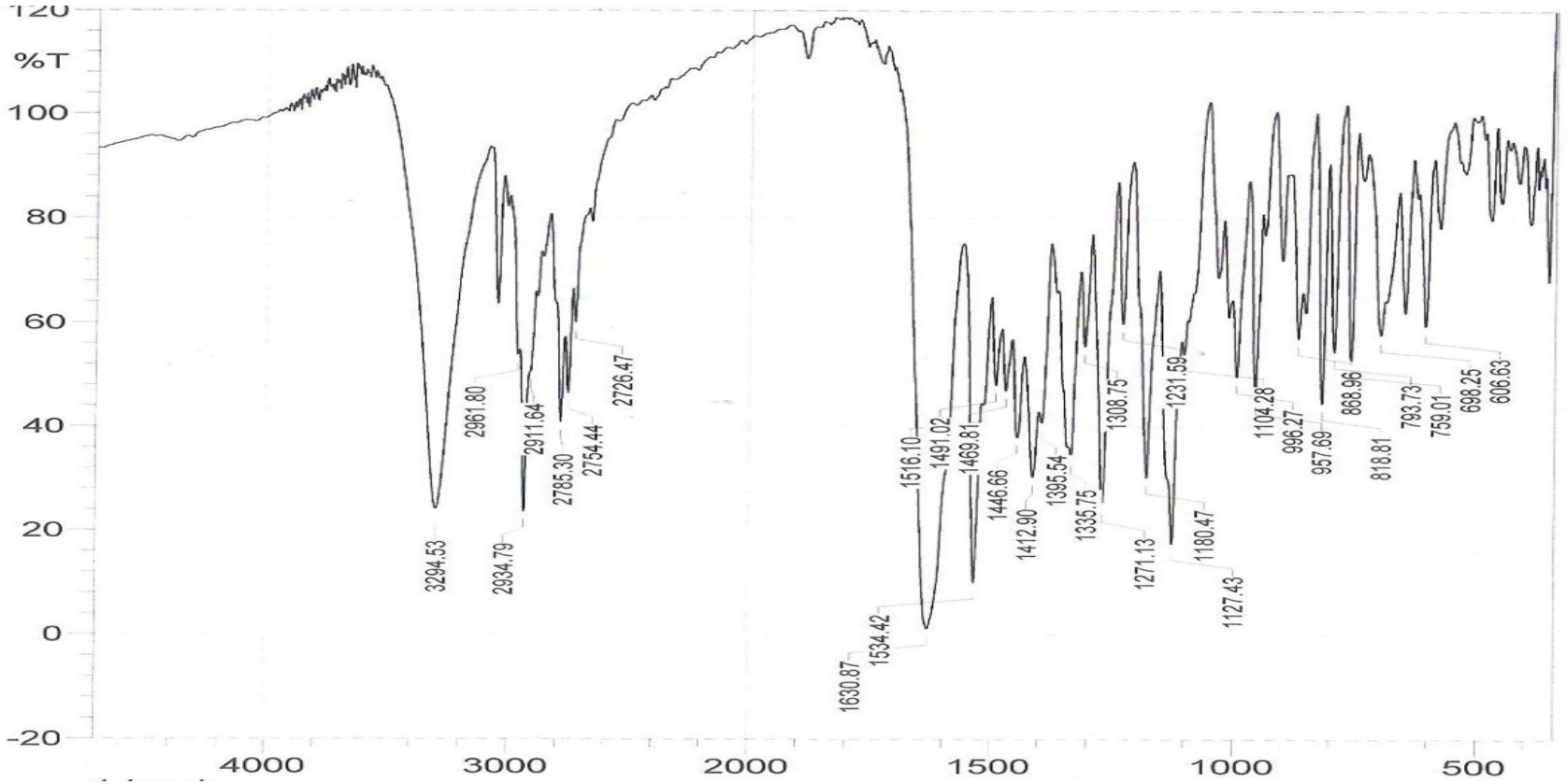
Concentration (µg/ml)	Absorbance
0	0
2	0.069
4	0.114
6	0.173
8	0.228
10	0.277



Compatibility studies:

- IR spectra matching approach was used for detection of any possible chemical interaction between the drug and the polymer.

IR Spectra of Paliperidone



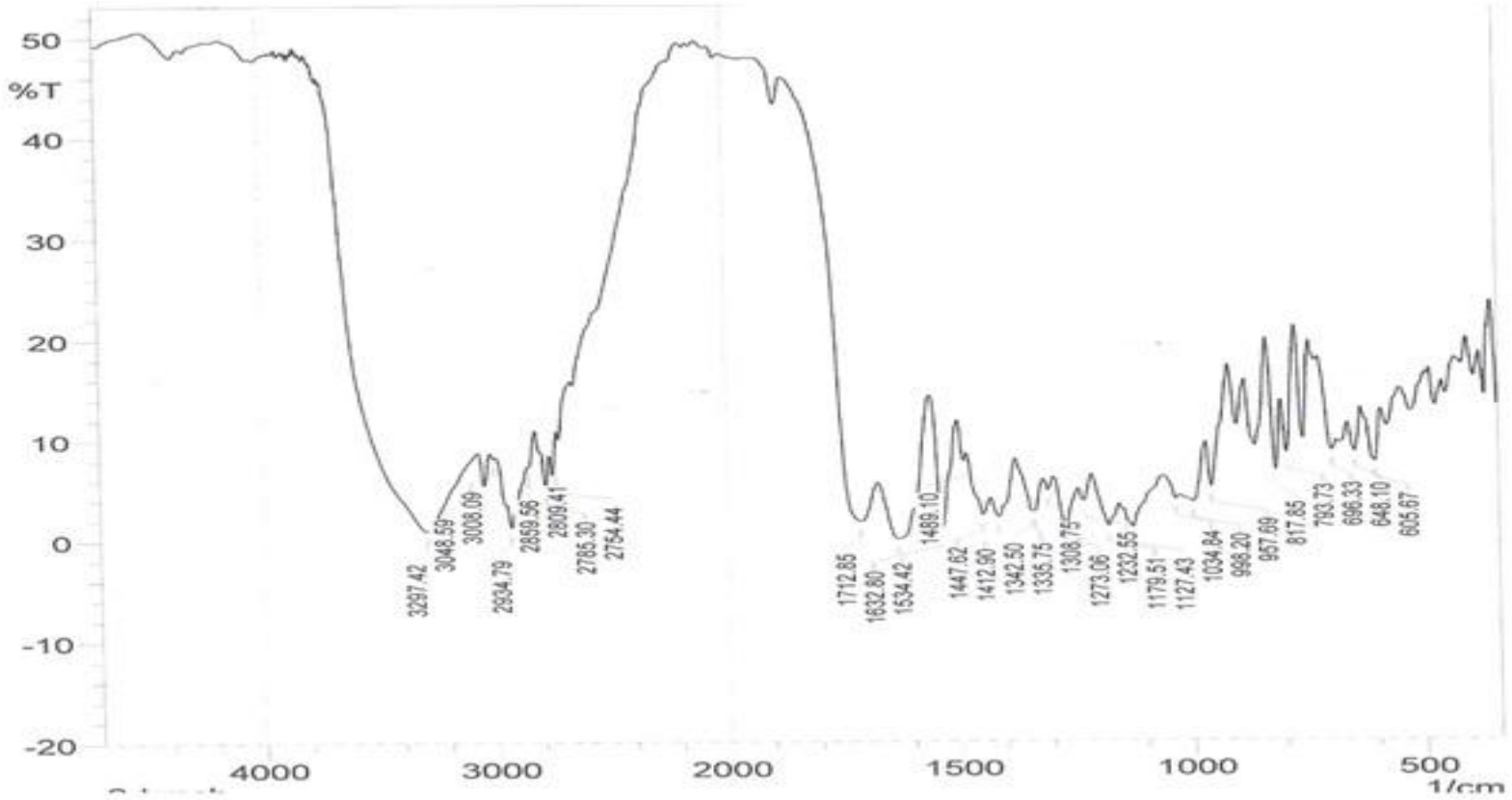
Interpretation of studied FTIR peaks with their characteristics functional groups

S.No	Peaks	Characteristic functional group
1	3294	NH Stretching
2	1630	C=O
3	1534	C=N
4	2911,2853	CH_2 Stretching
5	2961	CH_3 asymmetric stretching

Discussion:

It was found that the spectra of the drug with polymer showed all the characteristic peak of Paliperidone suggesting that there is no compatibility problem between the drug and polymer.

IR SPECTRA OF PALIPERIDONE+ *Azadirachta indica*



Preformulation Study:

FORMULATION CODE	ANGLE OF REPOSE	BULK DEDNSITY (g/ml)	TAPPED DENSITY (g/ml)	COMPRESSIBILITY INDEX (%)	HAUSNER'S RATIOS	VISCOSITY (poise)
F1	28°16'	0.625	0.899	30.47	1.43	1.0025
F2	30° 23'	0.681	0.883	22.87	1.29	1.0452
F3	32° 11'	0.423	0.521	18.80	1.23	1.1131
F4	33° 13'	0.431	0.552	21.92	1.28	0.7348
F5	33° 61'	0.617	0.819	24.66	1.32	0.7954
F6	34° 07'	0.625	0.830	24.69	1.33	0.8312
F7	38° 12'	0.602	0.809	25.58	1.34	0.7832
F8	38° 73'	0.421	0.529	20.41	1.25	0.8284
F9	39° 05'	0.683	0.889	23.17	1.30	0.8928
F10	26° 18'	0.512	0.623	17.81	1.21	0.9978
F11	27° 07'	0.458	0.537	14.71	1.17	1.0326
F12	39° 16'	0.465	0.571	18.56	1.22	1.1032
F13	33° 33'	0.620	0.891	30.41	1.43	0.5236
F14	34° 17'	0.615	0.811	24.16	1.31	0.6914
F15	34° 23'	0.601	0.807	25.52	1.34	0.7322

Discussion:

The results of the evaluation suggests that all the granules exhibit the good flow properties so the formulation blend was directly compressed to tablets

Evaluation of tablets

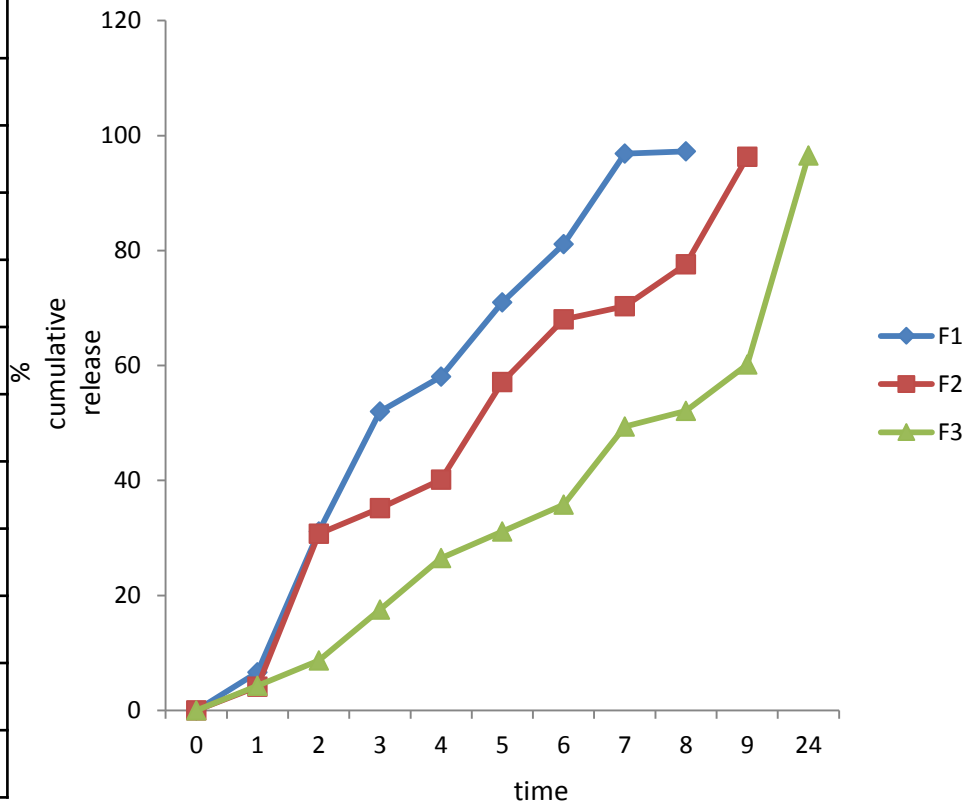
Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Average wt(mg)	Assay (%)
F1	0.31	4.0	0.523	199	95.12
F2	0.35	5.5	0.420	209	94.87
F3	0.41	6.0	0.413	203	95.02
F4	0.36	3.5	0.141	194	93.12
F5	0.39	5.0	0.159	198	92.09
F6	0.37	5.5	0.261	212	92.68
F7	0.40	4.5	0.102	200	90.12
F8	0.35	5.0	0.124	207	89.78
F9	0.39	6.0	0.198	203	90.03
F10	0.38	4.5	0.046	209	95.71
F11	0.35	5.5	0.047	201	96.29
F12	0.34	6.0	0.062	207	96.81
F13	0.41	3.5	0.212	208	94.71
F14	0.40	4.5	0.314	207	94.13
F15	0.36	5.0	0.282	209	95.11

Discussions:

The weight, thickness, hardness, friability, drug content and disintegration were all in the acceptable limits

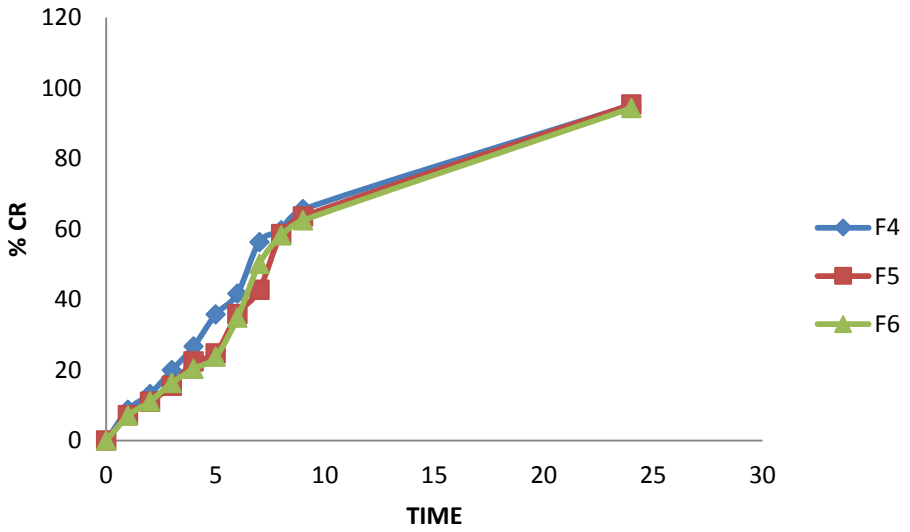
In-vitro dissolution studies:
1. Using HPMC

TIME	F1	F2	F3
0	0	0	0
1	6.6	4.12	4.30
2	31.12	30.75	8.71
3	52.01	35.20	17.51
4	58.07	40.12	26.51
5	70.98	57.10	31.10
6	81.12	68.01	35.81
7	85.88	70.33	49.40
8	87.27	77.60	52.09
9	91.95	86.32	60.15
24	95.60	95.96	96.50



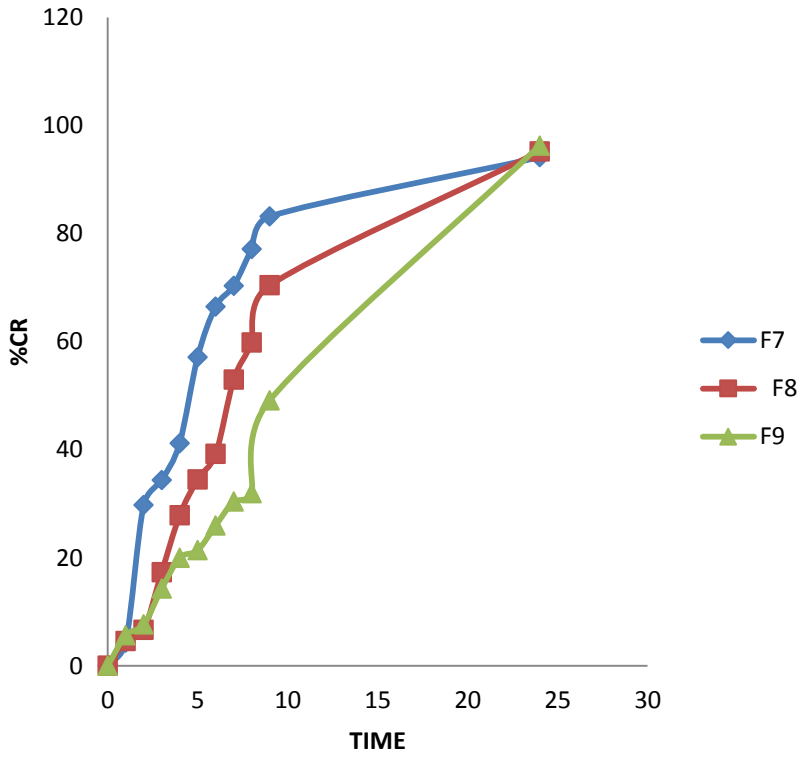
2. Using *Cassia roxburghii* Gum

TIME	F4	F5	F6
0	0	0	0
1	8.76	7.16	7.06
2	13.22	11.04	11.08
3	19.94	15.55	16.34
4	26.72	22.42	20.38
5	35.76	24.71	23.76
6	41.71	35.87	34.84
7	56.32	42.80	50.10
8	59.63	58.60	58.18
9	65.60	63.59	62.50
24	95.14	95.31	94.30



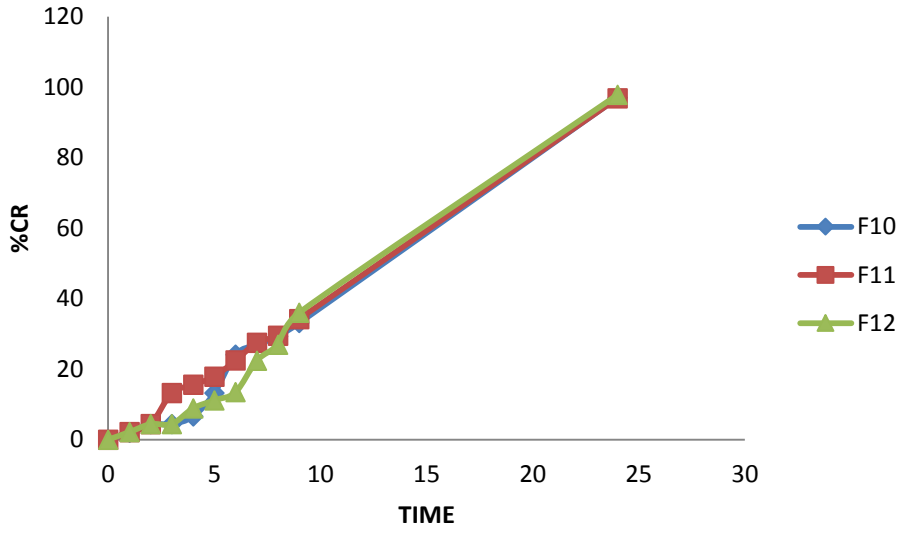
3. Using *Tamarindus indica* Gum

TIME	F7	F8	F9
0	0	0	0
1	4.30	4.58	5.62
2	29.76	6.65	7.63
3	34.35	17.31	14.27
4	41.20	27.83	19.98
5	57.13	34.51	21.38
6	66.47	39.20	25.98
7	70.34	52.94	30.41
8	77.10	59.84	31.95
9	83.17	70.41	49.13
24	94.12	95.20	96.27



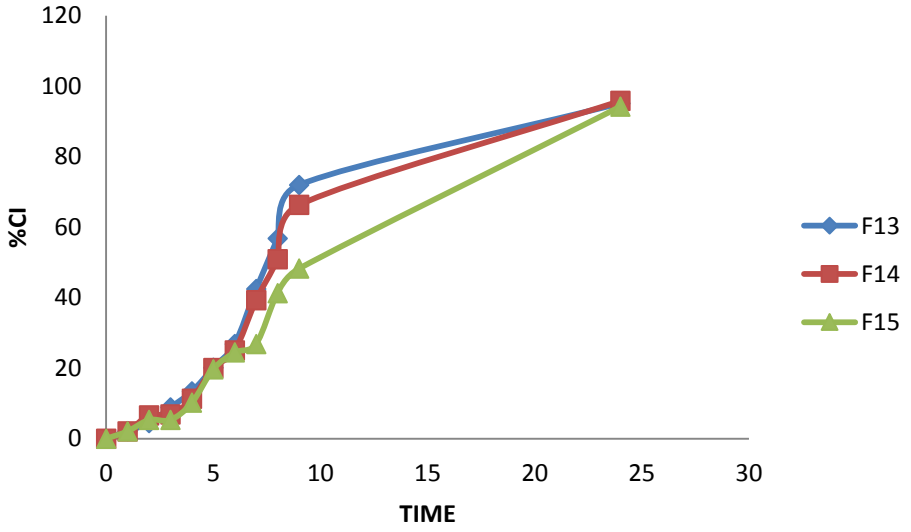
4. Using *Azadirachta indica* Gum

TIME	F10	F11	F12
0	0	0	0
1	2.01	2.20	2.15
2	4.40	4.41	4.41
3	4.39	13.23	4.45
4	6.62	15.55	8.89
5	13.21	17.90	11.16
6	24.11	22.45	13.46
7	26.90	27.49	22.38
8	29.28	29.52	26.98
9	33.10	34.24	36.02
24	96.97	96.86	97.80



5. Using *Manihot esculenta* Gum

TIME	F13	F14	F15
0	0	0	0
1	2.19	2.10	2.09
2	4.40	6.60	5.30
3	8.83	6.84	5.31
4	13.41	11.30	10.18
5	20.08	20.03	19.70
6	26.87	24.98	24.44
7	42.43	39.31	26.87
8	56.81	50.89	41.30
9	71.98	66.30	48.23
24	95.13	95.79	94.18



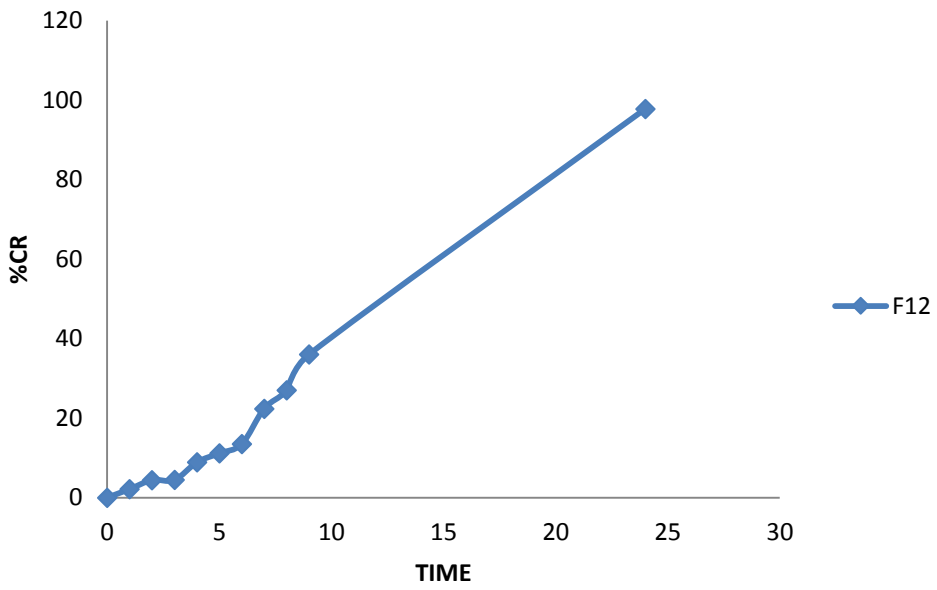
DISCUSSION

• All the fifteen formulations of paliperidone sustained release tablets were subjected to *in-vitro* release studies. These studies were carried out by using dissolution apparatus type II (paddle type) and the dissolution medium used was simulated gastric fluid (0.825M hydrochloric acid and 0.2% sodium hydroxide) for 24 hrs.

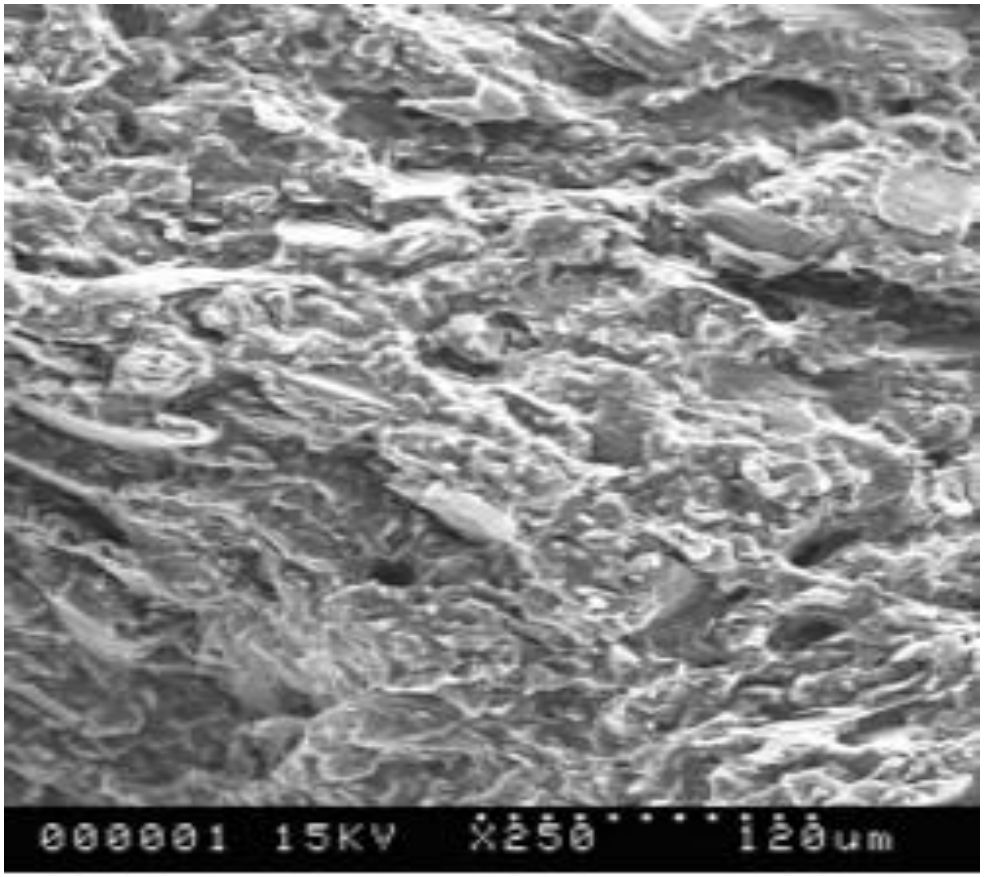
•Dissolution profiles of all formulations were compared by cumulative percentage drug release verses time. From dissolution results it was confirmed that the formulation F12 (neem gum75%) is the optimized formulation.

Dissolution Profile of the Optimised Formulation

TIME	FORMULATION F12
0	0
1	2.15
2	4.41
3	4.45
4	8.89
5	11.16
6	13.46
7	22.38
8	26.98
9	36.02
24	97.8



SEM analysis of optimised formulation(F12)



Drug Release Kinetic analysis:

FORMULATION CODE	ZERO ORDER (R^2)	FIRST ORDER (R^2)	HIGUCHI KINETICS (R^2)
F1	0.853	0.993	0.890
F2	0.924	0.831	0.734
F3	0.905	0.864	0.891
F4	0.934	0.904	0.836
F5	0.813	0.914	0.901
F6	0.993	0.834	0.807
F7	0.961	0.845	0.834
F8	0.834	0.901	0.806
F9	0.981	0.864	0.901

FORMULATION CODE	ZERO ORDER (R^2)	FIRST ORDER (R^2)	HIGUCHI KINETICS (R^2)
F10	0.986	0.780	0.926
F11	0.980	0.922	0.968
F12	0.955	0.711	0.940
F13	0.934	0.894	0.884
F14	0.983	0.914	0.861
F15	0.994	0.761	0.904

The regression coefficient value for zero order equation was found to be near to 1 revealing that the dissolution profile of the samples may follow zero order kinetics.

Stability Studies:

The tablets were loaded at accelerated condition at $40^0C \pm 2^0C/75\%$ RH±5% in a stability chamber.

SL. NO.	PARAMETERS	INITIAL	30th DAY	60th DAY	90th DAY
1	Physical appearance	Grey	Grey	Grey	Grey
2	Drug content (%)	96.81%	96.75%	96.34%	96.05%
3	Dissolution (%CR in 24th hour)	97.80%	97.38%	97.06%	96.92%

CONCLUSION

•From the IR spectra it is clear that there is no interaction between the drug and the gum

•Sustained release tablets of Paliperidone using natural polymers were successfully prepared by direct compression method.

•From the dissolution data, formulation F12 (neem75%) has the maximum release of the drug in 24 hours.

•The formulation F12 can be adopted for sustained release to improve the patient compliance and better disease management.

•From drug release kinetics data, the formulation follows zero order kinetics.

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Thank You……